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**Poster**

**PSTR001. Differentiation and Reprogramming Stem Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR001.01/A1

**Topic:** A.03. Stem Cells and Reprogramming

**Title:** A Reliable, Efficient, and Matrix-Free Method to Generate Midbrain Organoids from Human Pluripotent Stem Cells

**Authors: *L. H. CHEW**[1,2], A. ANONUEVO[2], N. IMANI FARAHANI[2], N. WILLIAMS[2], A. C. EAVES[2,3], S. A. LOUIS[2], E. KNOCK[2,4];
[1]STEMCELL Technologies, Vancouver, BC, Canada; [2]STEMCELL Technologies Inc., Vancouver, BC, Canada; [3]Terry Fox Lab., BC Cancer, Vancouver, BC, Canada; [4]Dept. of Biol., Simon Fraser Univ., Vancouver, BC, Canada

**Abstract:** Dopamine circuits originating from the midbrain have diverse functions that include regulating motor function, affect, and high-level executive function. Disruption of these circuits and/or dopaminergic neurons is implicated in diseases such as Parkinson's, schizophrenia, depression, and addiction. Animal models have been useful for studying these diseases, but the effectiveness of resulting clinical treatments has been variable. Human pluripotent stem cell (hPSC)-derived organoids permit the study of brain development, as well as disease etiology and progression in physiologically relevant tissue. Here we describe a matrix-free system to generate human midbrain organoids which can be applied to disease modeling of pathologies involving dopaminergic neurons. Single-cell suspensions of hPSCs (6 cell lines) were cultured for 6 days in AggreWell™800 plates containing organoid formation medium. The resulting organoids were cultured in midbrain organoid expansion medium from Day 6 - 25, and in midbrain organoid differentiation medium from Day 25 - 43. Finally, the organoids were cultured in maintenance medium from Day 43 onwards to support long-term culture. On Day 25, organoids were characterized for expression of floorplate precursor markers (LMX1A, EN1, and FOXA2) by RT-qPCR. On Day 50, organoids were characterized for expression of marginal zone dopamine neuron markers (TH, NURR1, GIRK2, and PITX3) by RT-qPCR and immunostaining. Compared to Day 25 dorsal forebrain patterned organoids, midbrain organoids expressed higher levels of LMX1A ($p = 0.0129$), EN1 ($p < 0.0001$), and FOXA2 ($p < 0.0001$) ($n = 6$ hPSC lines, 3 - 15 organoids per cell line) and lower expression of early dorsal forebrain marker PAX6 ($p = 0.0090$, $n = 6$ hPSC lines, 3 - 15 organoids per cell line, paired t-test). On Day 50, expression of TH ($p = 0.0301$), NURR1 ($p = 0.0222$), GIRK2 ($p = 0.0005$), and PITX3 ($p = 0.0284$) were elevated compared to dorsal forebrain patterned organoids ($n = 6$ hPSC lines, 3 - 15 organoids per cell line, paired t-test), while expression of mature dorsal forebrain marker TBR1 was comparatively lower ($p = 0.0001$, $n = 6$ hPSC lines, 3 - 15 organoids per cell line). Furthermore, bulk RNA-seq analysis provided a characteristic transcriptomic profile of day 50 midbrain organoids in comparison to dorsal forebrain organoids, confirming our RT-qPCR results. Immunofluorescent staining revealed abundant $TH^+$ neurons throughout the apical regions of the midbrain organoids. These results demonstrate the STEMdiff™ Midbrain Organoid Kit can

reproducibly generate tissue of an early human midbrain phenotype with the potential to model dopaminergic neurons of the substantia nigra region.

**Disclosures:** **L.H. Chew:** A. Employment/Salary (full or part-time); STEMCELL Technologies Inc. **A. Anonuevo:** A. Employment/Salary (full or part-time); STEMCELL Technologies Inc. **N. Imani Farahani:** A. Employment/Salary (full or part-time); STEMCELL Technologies Inc. **N. Williams:** A. Employment/Salary (full or part-time); STEMCELL Technologies Inc. **A.C. Eaves:** A. Employment/Salary (full or part-time); STEMCELL Technologies Inc. **S.A. Louis:** A. Employment/Salary (full or part-time); STEMCELL Technologies Inc. **E. Knock:** A. Employment/Salary (full or part-time); STEMCELL Technologies Inc.

**Poster**

**PSTR001. Differentiation and Reprogramming Stem Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR001.02/A2

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** The State Key Lab Grant for Young Scientists

**Title:** Identification of mitochondrial dynamics regulators during in vitro neural differentiation

**Authors: *W. ZHU**, Z. LIU;
CAS Ctr. for Excellence in Brain Sci. and Intelligence Technol., Shanghai, China

**Abstract:** Mitochondria are essential organelles that play important roles in energy metabolism, cell death, and signaling pathways. They continue to fuse, divide, and move within cells, thereby controlling their number, morphology, and subcellular distribution, which is known as mitochondrial dynamics. Aberrant mitochondrial fission during aging and in various neurodegenerative diseases leads to a progressive loss of mitochondrial function. However, the changes in mitochondrial dynamics and their involvement in the process of neuronal differentiation, which entails a significant transition in cell identity, remain largely unknown. In this study, we developed a molecular probe with improved performance and conducted high-resolution imaging of mitochondrial dynamics in an in vitro neuronal differentiation model using H9 human embryonic stem (ES) cells. Our imaging data revealed that mitochondrial dynamics, including number, morphology, fusion-fission, and movement undergo dramatic changes, at different stages of neuronal differentiation, including the ES stage, neural progenitor cell (NPC) stage, and neuron stage. To gain further insights, we employed transcriptome, total proteomics and mitochondrial proteomics to find potential new regulators of mitochondrial dynamics at different stages of this process. Surprisingly, well-known mitochondrial regulators such as MFN1, MFN2, OPA1, DNM1L, and MFF did not exhibit significant alterations in both transcription and protein levels, suggesting that they may function downstream of mitochondrial dynamics as basic machinery. Subsequently, we performed a CRISPR screen and successfully identified several novel candidates that regulate mitochondrial dynamics during neuronal

differentiation. Importantly, some of the identified candidates harbored genetic mutations associated with diverse neural diseases. Collectively, our findings established the importance of mitochondrial dynamics during neuronal differentiation and provided potential candidates for further investigation into the regulation of mitochondrial dynamics in both normal and diseased states.

**Disclosures: W. Zhu:** None. **Z. Liu:** None.

**Poster**

**PSTR001. Differentiation and Reprogramming Stem Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR001.03/A3

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** KIT GRANT 1711195884

**Title:** Rapid and Reliable Screening of Developmental Neurotoxicity Using efficient hiPSC-Neuron Differentiation

**Authors: *Y. CHUNG**[1,2], H. PARK[1], J. BAEK[1], W.-H. SHIN[1];
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**Abstract:** The human induced pluripotent stem cells (hiPSCs)-neuron differentiation technique is considered a reliable method for identifying the developmental neurotoxicity (DNT) of untested drugs and chemicals. In this study, we established a more efficient and rapid protocol for glutaminergic neurons differentiation by overexpressing neurogenin 2 (NGN2) and utilizing astrocytes as feeder cells in vitro. Immunostaining with β-III tubulin and MAP-2 revealed that the overexpression of NGN2 in hiPSC-derived neural precursor cells induced highly enriched glutamatergic neurons within two weeks. During neuronal differentiation from hiPSCs, we assessed the DNT of three chemicals (Chlorpyrifos, a pesticide; Bisphenol A, an endocrine disruptor; and PCB138, a persistent organic pollutant) associated with learning and memory. Immunocytochemistry and high-content imaging revealed that all three chemicals induced DNT, characterized by shortened neurite outgrowth and reduced synaptogenesis, at various IC50 concentrations in vitro. These results highlight the reliability, speed, and robustness of our automated DNT screening platform for identifying untested chemicals and drugs.

**Disclosures: Y. Chung:** None. **H. Park:** None. **J. Baek:** None. **W. Shin:** None.

**Poster**

**PSTR001. Differentiation and Reprogramming Stem Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR001.04/A4

**Topic:** A.03. Stem Cells and Reprogramming

**Title:** The downstream differentiation potential of human induced pluripotent stem cell-derived neural progenitor cells to forebrain neurons and astrocytes

**Authors:** A. MOOSA[1], ***J. KEIL**[1], S. A. LOUIS[1], A. EAVES[1,2], E. KNOCK[3,1]; [1]STEMCELL Technologies, Inc., Vancouver, BC, Canada; [2]BC Cancer, Terry Fox Lab., Vancouver, BC, Canada; [3]Biol., Simon Fraser Univ., Burnaby, BC, Canada

**Abstract:** Neural progenitor cells (NPCs) are characterized by their capacity to expand and generate the major differentiated cell types of the central nervous system (CNS), such as forebrain neurons and astrocytes. Cryopreserved CNS-type NPCs can serve as a reproducible starting point and provide flexibility and consistency for downstream differentiation. We have developed a protocol to scale up production of highly pure human induced pluripotent stem cell (hiPSC)-derived NPCs using the hiPSC SCTi003-A cell line. SCTi003-A hiPSCs were seeded on hESC-qualified Corning Matrigel®-coated plates in complete STEMdiff™ Neural Induction Medium + SMADi. Three weeks of daily feeds and weekly passaging resulted in an average of 27 NPCs per input iPSC, yielding > 500 million viable NPCs/batch. SCTi003-A-derived NPCs were then cryopreserved on day 21 in STEMdiff™ Neural Progenitor Freezing Medium at a density of 1.3 x $10^6$ cells/mL and stored at -196°C. After thawing, the majority of the NPCs expressed PAX6 (96.4 ± 3.4%) and SOX1 (91.5 ± 2.4%), and exhibited little spontaneous neuronal differentiation (3.5 ± 1.3% βIIITUB$^+$; mean ± SEM; n = 4). Thawed NPCs maintained in STEMdiff™ Neural Progenitor Medium and expanded for at least 5 passages displayed a 2.8 ± 0.5-fold increase (mean ± SEM; n = 4) in cell number/passage while retaining NPC phenotype (97.8 ± 1.3% PAX6$^+$SOX1$^+$). NPCs were differentiated immediately after thawing or after several passages to forebrain neurons or astrocytes using STEMdiff™ Forebrain Neuron or Astrocyte Differentiation Kits, respectively. NPCs differentiated immediately after thawing displayed high neurogenic differentiation towards forebrain neurons, as indicated by the high ratio of neuronal marker βIIITUB$^+$ (94.0 ± 0.8%) to two glial markers, glial fibrillary acidic protein (GFAP) and S100 calcium-binding protein B (S100B) (1.3 ± 0.7%; mean ± SEM; n= 4). The number of βIIITUB$^+$ cells steadily declined after each passage (34.0 ± 6.4% after 6 passages), while the number of cells positive for gliogenic markers GFAP/S100B increased (36.0 ± 4.9% after 6 passages; mean ± SEM; n = 4). Conversely, gliogenic differentiation to astrocytes immediately after thaw resulted in a pure population of GFAP$^+$ (82.4 ± 5.0%) and S100β$^+$ cells (80.8 ± 4.6%), with low levels of immature neuron marker doublecortin (DCX) (3.2 ± 1.1%; mean ± SEM; n = 4), which were retained for up to 10 passages. In summary, we have generated highly pure, expandable, and multipotent hiPSC-derived NPCs suitable for large-scale neural research, and investigated their downstream differentiation potential over time to assess the acceptable windows to successfully generate neurogenic or gliogenic derivatives.

**Disclosures:** **A. Moosa:** A. Employment/Salary (full or part-time); STEMCELL Technologies, Inc. **J. Keil:** A. Employment/Salary (full or part-time); STEMCELL Technologies. **S.A. Louis:** A. Employment/Salary (full or part-time); STEMCELL Technologies. **A. Eaves:** A.

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**Poster**

**PSTR001. Differentiation and Reprogramming Stem Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR001.05/A5

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** R01ES033636 (to LMI and ARM)

**Title:** Impact of PFAS on human cortical organoid neurodevelopment

**Authors: *G. GOMEZ**[1], L. MOLONY[1], K. KIRKWOOD[3], A. FALLS[3], E. BAKER[3], Z. LIEW[4], A. MOUTRI[2], L. IAKOUCHEVA[1];
[2]Dept. of Cell. & Mol. Med. and Dept. of Pediatrics, [1]Univ. of California San Diego, San Diego, CA; [3]Dept. of Chem., Univ. of North Carolina, Chapel Hill, NC; [4]Dept. of Envir. Hlth. Sci. and Yale Ctr. for Perinatal, Pediatric and Envir. Epidemiology, Yale Sch. of Publ. Hlth., New Haven, CT

**Abstract:** Per- and polyfluoroalkyl substances (PFAS) are a large family of man-made persistent contaminants present in industrial and commercial products. PFAS are very resistant to degradation and recalcitrant in the environment; they were detected in drinking water, wildlife and human samples showing variable but very long half-lives. PFAS can cross the blood-brain barrier and have been found in placenta and umbilical cord. Epidemiological findings suggest associations with impaired fetal and postnatal growth. Neurodevelopmental in-vitro and in-vivo studies showed that PFAS exposure affects animal birth weight, behavior, and molecular mechanisms linking them to glutamatergic, cholinergic and dopaminergic systems. The aim of this study is to investigate how the exposure to PFAS impacts early brain development using human-derived models. Human cortical organoids (hCOs) were generated from human iPSCs and exposed to different concentrations of Perfluorooctanesulfonic acid (PFOS) and Perfluorooctanoic acid (PFOA), and other two known neurotoxins, chlorpyrifos (CPF) and camptothecin (CPT). Organoids were collected at different time points for early apoptosis and DNA fragmentation assays. We observed an increase in early apoptosis and DNA fragmentation induced by the exposure to CPF and CPT. We also observed an increased PFOS-induced apoptosis in one-month old organoids after one and three weeks of chronic exposure. We found that two-week old organoids appeared to have higher basal levels of apoptosis, and they were more sensitive to these compounds. To evaluate any transcriptional dysregulation elicited by PFAS exposure, we exposed the organoids for one month and performed a bulk RNA-seq analysis. Preliminary results suggest that translation-related processes including “cytoplasmic translation”, “ribosome biogenesis”, and “ncRNA processing” may be dysregulated in PFOS-exposed organoids. Finally, the liquid chromatography, ion mobility spectrometry, and mass spectrometry was used to evaluate the presence of these PFAS in organoids and their media.

Quantification demonstrated that organoids could absorb these compounds and that the ratio of PFOS in hCO:media was higher than that of PFOA, suggesting increased tissue penetration or accumulation of PFOS compared to PFOA. In conclusion, we developed an experimental design for the exposure of hCOs to PFAS, suitable for evaluating changes in cellular processes like apoptosis and gene expression. Our results suggest that PFOS may have a dose-dependent pro-apoptotic effect and impact gene expression in the developing hCOs, which would require replication in hCO derived from additional cell lines.

**Disclosures:** **G. Gomez:** None. **L. Molony:** None. **K. Kirkwood:** None. **A. Falls:** None. **E. Baker:** None. **Z. Liew:** None. **A. Moutri:** None. **L. Iakoucheva:** None.

**Poster**

**PSTR001. Differentiation and Reprogramming Stem Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR001.06/A6

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** INPer 212250-3230-21214-03-16

**Title:** Understanding the possible role of prolactin and its receptor during cortical neuronal differentiation of mouse embryonic stem cells

**Authors:** ***O. MARTÍNEZ**[1], D. COLIN-LAGOS[1], X. RAMIREZ-MEZA[1], G. CASTILLO-VILLALON[1], A. CASTILLA LEON[2], D. AVILA-GONZALEZ[1], G. GARCIA-LOPEZ[1], A. MOLINA-HERNANDEZ[1], W. PORTILLO[2], N. DIAZ[1];
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**Abstract:** The cerebral cortex governs complex functions such as language and memory. However, its embryonic development has remained elusive due to the lack of suitable experimental models. Embryonic stem cells (ESCs), characterized by self-renewal and the ability to differentiate into several cell types, offer an alternative for studying central nervous system development. Thus, we can investigate the role of several molecules, such as prolactin (PRL), a hormone with over 300 physiological functions in vertebrates associated with maternal behavior and adult neurogenesis. Nonetheless, its possible involvement during embryonic cerebral cortex development remains unknown. Here, we determine the presence of the PRL receptor and the hormone´s effect on the differentiation of mouse ESCs into cortical neurons. We found an increase in the PRL receptor expression that correlated with the early emergence of neural stem cells, which was downregulated in the GFAP-positive cells at late stages in the protocol. On the other hand, when we tested several PRL concentrations during the proliferation and differentiation stages in a neural protocol, we did not find any statistical differences with the PRL treatments during proliferation in the number of Sox2+ and double Nestin+ and Edu+ cells. Also, all hormone concentrations induced an increasing trend in β-tubulin-III+ cells, but without

reaching statistical significance. Interestingly, we observed a decrease in Map2+ and NeuN+ cells with the highest (20 mM) and lowest (0.2 mM) PRL concentrations, respectively. The PRL treatments did not yield any changes during the differentiation stage compared to the control group. Our study provides insights into the effects of PRL on the differentiation of mouse ESCs into cortical neurons, shedding light on the possible involvement of PRL and its receptor in corticogenesis.

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**Poster**

**PSTR001. Differentiation and Reprogramming Stem Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR001.07/A7

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** National Key Research and Development Program of China((2018YFA0108000 to Y.C. and 2021YFF0703802 to W.W.))
STI2030-Major Projects (2021ZD0200900 to Y.C.)
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UniXell R&D Innovation Cooperation Program (DA001-RD202101 to Y.C.)

**Title:** Mapping of clonal lineages across developmental stages in human neural differentiation

**Authors: *Z. YOU**, L. WANG, W. WEI, Y. CHEN;
Chinese Acad. of Sci., Shanghai, China

**Abstract:** The cell lineages across developmental stages remain to be elucidated. Here, we developed single-cell split barcoding (SISBAR) that allows clonal tracking of single-cell transcriptomes across stages in an in vitro model of human ventral midbrain-hindbrain differentiation. We developed ‘‘potential-spective’’ and ‘‘origin-spective’’ analyses to investigate the cross-stage lineage relationships and mapped a multi-level clonal lineage landscape depicting the whole differentiation process. We uncovered many previously uncharacterized converging and diverging trajectories. Furthermore, we demonstrate that a transcriptome-defined cell type can arise from distinct lineages that leave molecular imprints on their progenies, and the multilineage fates of a progenitor cell-type represent the collective

results of distinct rather than similar clonal fates of individual progenitors, each with distinct molecular signatures. Specifically, we uncovered a ventral midbrain progenitor cluster as the common clonal origin of midbrain dopaminergic (mDA) neurons, midbrain glutama-tergic neurons, and vascular and leptomeningeal cells and identified a surface marker that can improve graft outcomes.

**Disclosures:** **Z. You:** None. **L. Wang:** None. **W. Wei:** None. **Y. Chen:** None.

**Poster**

**PSTR001. Differentiation and Reprogramming Stem Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR001.08/A8

**Topic:** A.03. Stem Cells and Reprogramming

**Title:** Rapid and consistent generation of functional microglia from reprogrammed hiPSC to study mechanisms in neurodegeneration and neuroinflammation.

**Authors: *P. R. BARTON**[1], C. FAIRBAIRN[1], E. YATES[1], R. HICKMAN[2], P. PERAC[2], B. KLAPHOLZ[2], S. MILDE[2], R. O'REILLY[2], H. GARNETT[2], M. RAMAN SRIVASTAVA[2], F. PATELL-SOCHA[2], E. CORRIE[3], E. V. JONES[3], T. MOREAU[2], W. BERNARD[1], M. METZAKOPIAN[2], M. KOTTER[2];
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**Abstract:** Microglia are the tissue-resident macrophages of the brain, accounting for 75-80% of leukocytes and 10-15% of total cells within the central nervous system (CNS). They survey neuronal function, play roles in neurogenesis, synaptic remodelling, are the first responders to infection, and are thereby implicated in various CNS diseases. The life sciences sector relies predominantly on rodent models to mimic disease states for drug discovery. However, animal models do not always recapitulate human cell and disease phenotypes. To bridge this translational gap, several *in_vitro* human models have been developed for the study of microglia, most typically primary microglia extracted directly from either embryonic, neonatal or adult tissue. However, primary cells are limited in supply, difficult to source, and often show donor-to-donor and user variability. There is a need for functional, consistent, scalable disease-relevant human microglia cells for neuroimmune research and the development of therapeutic or preventive strategies for neurodegeneration. We used transcription factor mediated precision cellular reprogramming technology, opti-ox™, to rapidly and consistently generate mature, functional, and physiologically relevant microglia, named ioMicroglia, from hiPSCs, at scale. ioMicroglia, 10 days post-revival, display typical morphology and express key phenotypic markers including TMEM119, P2RY12, and IBA1. RNA sequencing demonstrates that ioMicroglia have a transcriptomic signature similar to primary adult and foetal microglia. ioMicroglia also express the complement-derived chemotaxin C5a receptor, which permits migration towards sites of inflammation and injury. Furthermore, ioMicroglia display both

random chemokinetic movement and directional chemotaxis in response to C5a and a C5a gradient, in a dose dependent manner. Consistent phagocytic and cytokine secretion functionality, with various stimuli, including amyloid beta, has been demonstrated for ioMicroglia, across multiple independent laboratories within industry and academia, highlighting the experimental reproducibility of ioMicroglia. Importantly, ioMicroglia can be co-cultured with neurons to more closely mimic *in_vivo* brain function. In conclusion, with opti-ox™ precision cellular reprogramming, hiPSCs are rapidly converted into functional microglia offering a robust and scalable source of human microglia which can be used as a relevant in_vitro model to investigate the role of the CNS's immune system in health and disease, and to develop novel therapies for neuroinflammation.

**Disclosures:** **P.R. Barton:** A. Employment/Salary (full or part-time); bit.bio. **C. Fairbairn:** A. Employment/Salary (full or part-time); bit.bio. **E. Yates:** A. Employment/Salary (full or part-time); bit.bio. **R. Hickman:** A. Employment/Salary (full or part-time); bit.bio. **P. Perac:** A. Employment/Salary (full or part-time); bit.bio. **B. Klapholz:** A. Employment/Salary (full or part-time); bit.bio. **S. Milde:** A. Employment/Salary (full or part-time); bit.bio. **R. O'Reilly:** A. Employment/Salary (full or part-time); bit.bio. **H. Garnett:** A. Employment/Salary (full or part-time); bit.bio. **M. Raman Srivastava:** A. Employment/Salary (full or part-time); bit.bio. **F. Patell-Socha:** A. Employment/Salary (full or part-time); bit.bio. **E. Corrie:** A. Employment/Salary (full or part-time); Medicines Discovery Catapult. **E.V. Jones:** A. Employment/Salary (full or part-time); Medicines Discovery Catapult. **T. Moreau:** A. Employment/Salary (full or part-time); bit.bio. **W. Bernard:** A. Employment/Salary (full or part-time); bit.bio. **M. Metzakopian:** A. Employment/Salary (full or part-time); bit.bio. **M. Kotter:** A. Employment/Salary (full or part-time); bit.bio.

**Poster**

**PSTR001. Differentiation and Reprogramming Stem Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR001.09/A9

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** CIHR
VSRP

**Title:** Investigating the function of the musashi family of RNA-binding proteins during zebrafish retinal regeneration

**Authors: *J. STULBERG**[1,2], V. TROPEPE[1];
[2]Cell & Systems Biol., [1]Univ. of Toronto, Toronto, ON, Canada

**Abstract:** The mature zebrafish retina contains Müller glia (MG), a relatively quiescent radial glial cell population with stem cell properties capable of regenerating the retina in response to acute lesions. In response to injury, MG cells will undergo a genomic reprogramming event,

which gives them the ability to produce new cells to repair the retina. Using publicly available single-cell RNA-sequencing data, we found that msi1b is expressed in both quiescent and reprogrammed MG cells suggesting that it may play a potential role in regulating stem cell behavior and/or MG reprogramming. We characterized the expression profile of all musashi isoforms (msi1a, msi1b, msi2a, and msi2b) and found that while all were expressed in quiescent and reprogrammed MG cells, msi1b exhibited the highest expression level. Consequently, we used CRISPR/Cas9 to generate both transient msi1b F0 knockouts and stable germline mutants and found that msi1b alone is not necessary for MG reprogramming. Although the musashi protein isoforms showed relatively low amino acid sequence homology, the conservation of their RNA binding domains indicated potential redundancy in gene function, suggesting that a single knockout may not yield an observable phenotype. To address this, we performed knockouts of all four musashi isoforms in F0 fish and discovered retinal embryonic defects, indicating some redundancy in gene function among the musashi isoforms. We are testing this hypothesis by determining the minimal number of isoforms required for normal retinal development and MG reprogramming by generating combinatorial knockouts.

**Disclosures:** **J. Stulberg:** None. **V. Tropepe:** None.

**Poster**

**PSTR001. Differentiation and Reprogramming Stem Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR001.10/A10

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** California Institute for Regenerative Medicine (CIRM)

**Title:** Defects in cell polarity of Mucopolysaccharidosis type III (MPS III) forebrain neurons

**Authors:** ***J. HERNANDEZ**, J. ACEVEDO, P. MATHEWS, M. IACOVINO;
The Lundquist Inst., Torrance, CA

**Abstract:** Mucopolysaccharidosis type III A and B (MPS IIIA/B) are rare pediatric inherited lysosomal storage diseases that causes the progressive degeneration of the central nervous system. Children with MPS III experience severe intellectual disability, developmental regression, behavioral issues, loss of brain volume and neuroinflammation soon after birth. MPS IIIA and B are caused by the loss of a lysosomal enzymes needed to degrade glycosaminoglycan (GAG), a complex sugar molecule. Children diagnosed with MPS III typically live until the second or third decade of life, since there is currently no effective treatment that exists. The early lysosomal and neurological mechanisms at play in MPS III remains to be fully understood. In our preliminary work, we utilized mass spectrometry to run a whole proteome analysis on brain organoids between a healthy patient and two MPS IIIB patients. Our mass spectrometry data show that several genes involved in the process of neurite formation are dysregulated in MPS IIIB brain organoids. Specifically, many proteins involved in lamellipodia formation (VASP,

RAPH1, TUBB3, SNX2, WASF2, and BRSK2), in filopodia formation (IRSP53, FSCN1, NAV3, and FAK2), and axonal guidance (THY1, SEMA3A, SEMA5B, and SEMA3C) were significantly dysregulated in disease brain organoids when compared to healthy controls. To validate our findings, we differentiated MPS IIIA iPSC into forebrain neurons to evaluate neurite formation. Using MAP2 staining, we showed that approximately 60% of the MPS IIIA forebrain neurites do not properly develop dendrites and axons, while only 20% of healthy control neurons are in this stage, thus failing to advance to stage 2 and stage 3 during neuronal differentiation. We are measuring the length, thickness, and branching of the neurites in the MPS IIIA and healthy control forebrain neurons to further characterize MPS neuronal defects.

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**Poster**

**PSTR001. Differentiation and Reprogramming Stem Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR001.11/A11

**Topic:** A.03. Stem Cells and Reprogramming

**Title:** Late-stage neuronal development and synaptic maturation of iPSC-derived excitatory neurons

**Authors: *W. LIN**[1], S. KUDO[1], S. SHIOMOTO[1], S. YAMADA[1], K. MURAMATSU[1], K. SAKAGUCHI[1], Y. EGUCHI[1], Y. SEKINO[2,3], T. HOSOYA[1];
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**Abstract:** Studying synapse formation and alterations in neuronal cell cultures would help to predict drug effects and pathological conditions of neurotransmission. Human induced pluripotent stem cell (iPSC)-derived neurons are particularly promising for developing *in vitro* disease models and assays. However, synaptic maturation has been reportedly difficult to reproduce in iPSC-derived neurons, which has limited their use compared to primary rodent neurons. Recently, we successfully generated functionally mature iPSC-derived neurons by a transcription factor (TF)-based differentiation method that accelerates neurogenesis, thus offering an unprecedented opportunity to address further progression into late developmental stages. In the present study, we demonstrate by a comprehensive time-course characterization that TF-induced iPSC neurons exhibit maturation of dendritic spines and synapses at around DIV 70, as shown by RNA-sequencing, immunocytochemistry, and electrophysiological evaluation using high-density microelectrode arrays (HD-MEA). The neurons showed postnatal-like transcriptional features of brain development, including the upregulation of mature brain-specific markers such as 4R tau. The formation of adjacent presynaptic Synapsin I and postsynaptic drebrin clusters along MAP2-positive dendrites indicated the establishment of synaptic connections. Concurrent HD-MEA recordings revealed a time-dependent increase in network activity and complexity. Moreover, glutamate exposure induced NMDA receptor activity-

dependent drebrin exodus, which suggests that TF-induced iPSC neurons successfully acquire the molecular mechanism underlying synaptic plasticity as known in rodents. Finally, these results allowed us to develop a deep learning-based automated imaging assay of synaptic marker density in TF-induced iPSC neurons, which would contribute to the future development of drug screening platforms. Overall, we propose that mature TF-induced iPSC neurons are powerful tools to study human synapses and would be valuable for modeling neurocognitive and neurodevelopmental disorders.

**Disclosures:** **W. Lin:** None. **S. Kudo:** None. **S. Shiomoto:** None. **S. Yamada:** None. **K. Muramatsu:** None. **K. Sakaguchi:** None. **Y. Eguchi:** None. **Y. Sekino:** F. Consulting Fees (e.g., advisory boards); Ricoh Company, Ltd. **T. Hosoya:** None.

**Poster**

**PSTR001. Differentiation and Reprogramming Stem Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR001.12/A12

**Topic:** A.03. Stem Cells and Reprogramming

**Title:** Cultural Characteristics of Human Microglia from APOE-TREM2 Modified Induced Pluripotent Stem Cells

**Authors:** R. ALVAREZ[1], ***K. XU**[2], A. JOHNSON[1], M. HENDRICKSON[1], S. DU[1], K.-D. CHOI[1];
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**Abstract:** The Human microglia are essential immune cells that function to regulate homeostatic microenvironment of the central nervous system (CNS). Uncontrolled dysfunction of microglia is implicated in neurodegenerative diseases such as Alzheimer's Disease (AD). For AD incident, a specific APOE allele and TREM2 are known to AD risk factors. Due to restricted availability for primary microglia from healthy and diseased tissues, generation of human microglia from gene modified induced pluripotent stem cells (iPSCs) will be a tailored source for pharmaceutical research and applications. The present study demonstrates efficient generation of homogeneous human microglia from iPSCs. We differentiated hematopoietic progenitors from wild type (WT) and APOE-TREM2 modified iPSCs, and then specified further into microglia fate. To characterize and evaluate features of microglia, APOE-TREM2 modified microglia were compared to WT microglia for culture morphology, lineage specific marker expression, and phagocytosis of amyloid β (Aβ) peptide. Our results showed that APOE-TREM2 modified microglia were less adherent with shorter ramified morphologies, lower expression of homeostatic surface markers such as P2RY12, CX3CR1 and TMEM119 as well as impaired phagocytosis of amyloid β (Aβ). Our results suggest that human microglia from APOE-TREM2 modified hiPSCs induce transition of microglia into disease associated state. Therefore, gene modified hiPSC-based microglia can be a reproducible strategy for disease modeling and drug screening for AD.

**Disclosures:** **R. Alvarez:** A. Employment/Salary (full or part-time); BRAINXELL INC. **K. Xu:** A. Employment/Salary (full or part-time); BRAINXELL INC. **A. Johnson:** A. Employment/Salary (full or part-time); BRAINXELL INC. **M. Hendrickson:** A. Employment/Salary (full or part-time); BRAINXELL INC. **S. Du:** A. Employment/Salary (full or part-time); BRAINXELL INC. **K. Choi:** A. Employment/Salary (full or part-time); BRAINXELL INC.

**Poster**

**PSTR001. Differentiation and Reprogramming Stem Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR001.13/A13

**Topic:** A.03. Stem Cells and Reprogramming

**Title:** Scaled out human iPSC derived sensory neuron production

**Authors: *C. HILL**, S. PAULSON, M. DAU, V. TRUONG, P. WALSH;
Anatomic Inc., Minneapolis, MN

**Abstract:** More effective, personalized treatment options are urgently required for chronic pain which affects 1 in 5 people worldwide. A scalable, rapid, and reproducible protocol to produce sensory neurons from multiple human induced pluripotent stem cell (hiPSC) lines would aid in better understanding the genetic basis of pain and accelerate drug discovery platforms for novel analgesics. In this study, three different hiPSC lines (WT- female, WT- male, Pain agnosia-female) were differentiated using small molecules and growth factors that modulated different signaling pathways through daily media exchanges. Different developmental stages were recapitulated within the ectodermal lineage over seven days until BRN3A+/PRPH+ and ISLET1+/TUJ1+ sensory neurons developed at a purity of greater than 95%. Initially, single cell seeding density titrations were carried out in 6 well plates to establish the best concentration for optimal differentiation before sensory neuron production was scaled up in flask format and cryopreserved. Sensory neurons were then thawed and matured for one week before being characterized via immunocytochemistry and qPCR for the pan-sensory neuron ion channels: NaV1.7, NaV1.8, NaV1.9, TRPV1, CAV3.2, P2RX3, and TRKA. The three different donor lines were found to have similar gene expression profiles. Lastly, sensory neurons derived from each line were matured on multi-electrode array (MEA) plates and baseline activity was recorded weekly over 4 weeks to look at functional differences in donor lines. These findings show a rapid 7 day directed differentiation protocol can be applied to multiple hiPSC donor lines and successfully produce functional, sensory neurons for downstream assays. This process would allow researchers to test many biological samples with diverse backgrounds to better understand the genetic differences in pain and develop more effective, personalized treatment options.

**Disclosures:** **C. Hill:** A. Employment/Salary (full or part-time); Anatomic, Inc. **S. Paulson:** A. Employment/Salary (full or part-time); Anatomic, Inc. **M. Dau:** A. Employment/Salary (full or part-time); Anatomic, Inc. **V. Truong:** A. Employment/Salary (full or part-time); Anatomic, Inc.

E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anatomic, Inc. **P. Walsh:** A. Employment/Salary (full or part-time); Anatomic, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anatomic, Inc.

**Poster**

**PSTR001. Differentiation and Reprogramming Stem Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR001.14/A14

**Topic:** A.03. Stem Cells and Reprogramming

**Title:** Generation of Human Endothelial Cells for Integration of Pericytes and Regional Specific Astrocytes to Mimic in vitro Blood Brain Barrier Model from Human Induced Pluripotent Stem Cells

**Authors: *K.-D. CHOI**, K. XU, L. LAWSON, J. HJELMHAUG, R. ALVAREZ, S. HANSON, M. HENDRICKSON, S. DU;
RnD, BrainXell Inc., Madison, WI

**Abstract:** The Human blood brain barrier (BBB) is a protective microvascular system that encapsulates the central nervous system (CNS) and is crucial for maintaining a homeostatic environment for the brain. Breakdown of the BBB's integrity is implicated in several neurodegenerative diseases: Alzheimer's Disease (AD), Parkinson's disease (PD), Amyotrophic lateral Sclerosis (ALS), Multiple Sclerosis (MS), and Hunting's disease, to name a few. Unfortunately, availability of primary human BBB and its cellular components are limited. Thus, precise recapitulation of human BBB in vitro is an efficient tool for pharmaceutical research and applications. This study demonstrates efficient methods to differentiate human induced pluripotent stem cells (hiPSCs) into three cellular components to mimic human BBB in vitro. We differentiated, and identified each cell type by morphology and specific marker expression as follows: VE-cadherin$^{+}$ZO1$^{+}$Glut1$^{+}$ endothelial cells (EC), PDGFR$\beta^{+}$NG2$^{+}$ pericytes (PC) and GFAP$^{+}$ astrocytes (AC). To characterize and assess barrier function of our human BBB in vitro, we optimized a tri-culture system with the hiPSC derived EC, PC, and AC, and measured the system's transepithelial/ transendothelial electrical resistance (TEER) as well as permeability. Our TEER results indicate, the hiPSC-derived triculture of ECs, PCs, and ACs formed a monolayered which like a barrier. Because of its functional properties, the human BBB, is emerging as a critical target for pharmaceutical approaches. Therefore, hiPSC-based BBB modeling can be a reproducible strategy for disease modeling and drug screening in neurodegenerative diseases.

**Disclosures: K. Choi:** A. Employment/Salary (full or part-time); BRAINXELL INC. **K. Xu:** A. Employment/Salary (full or part-time); BRAINXELL INC. **L. Lawson:** A. Employment/Salary (full or part-time); BRAINXELL INC. **J. Hjelmhaug:** A. Employment/Salary (full or part-time); BRAINXELL INC. **R. Alvarez:** A. Employment/Salary

(full or part-time); BRAINXELL INC. **S. Hanson:** A. Employment/Salary (full or part-time); BRAINXELL INC. **M. Hendrickson:** A. Employment/Salary (full or part-time); BRAINXELL INC. **S. Du:** A. Employment/Salary (full or part-time); BRAINXELL INC.

**Poster**

**PSTR001. Differentiation and Reprogramming Stem Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR001.15/A15

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** Fast-track (Phase IIa) SBIR 5R44EY027654 (I.N., Lineage Cell Therapeu*cs)
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R44EY027654, PI Nasonkin
NIH grant (R01 EY031834), PI: M Seiler

**Title:** Retina organoids develop photoreceptors and improve visual function after long distance shipping and transplanted into RCS rats with RPE dysfunction

**Authors: *B. LIN**[1], R. K. SINGH[2], M. J. SEILER[3], I. O. NASONKIN[4];
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**Abstract:** Purpose. Retinal organoids (RO) derived from human embryonic stem cells (hESC) were shipped by flight to another facility using a special device and protocol. Organoids survival and visual improvement was studied after transplanted into immunodeficient Royal College of Surgeons (RCS) rats without the support of RPE, a rat model of retinal degeneration caused by RPE dysfunction. Methods. hESC-ROs were differentiated from the hESC line H1 (WA01. 30 - 70 day of differentiation) and shipped with a special device to another location, and then transplanted into the subretinal space of RCS rats, aged 44-76 days. Before the transplantation, retinal organoids were analyzed by qPCR and immunofluorescence. The development of transplant organoids *in vivo* in relation to the host was examined by optical coherence tomography (OCT). Visual function was assessed by optokinetic testing (OKT) and superior colliculus (SC) electrophysiological recording. Cryostat sections were analyzed for various retinal, synaptic and donor markers. Results. Retinal organoids showed similar gene expression to human fetal retina Transplanted rats demonstrated significant improvement in visual function compared to RCS non-surgery and sham surgery controls by optokinetic testing (up to 6 months post surgery) and electrophysiological SC recordings (6-8 months post surgery). 2/8 rats with transplants showed responses to a flash of light with SC recording, while AMC and sham showed no response to the same light intensity. The transplanted organoids survived more than 8.2 months, developed photoreceptors with inner and outer segments, and other retinal cells; and were well-integrated within the host. Conclusions. Our results showed that using our special device and protocol, the hESC derived retinal organoids can be shipped over long distance, and

capable of survival and visual improvement after transplanted into the RD rats, even with host's dysfunctional RPE. Our findings suggest that transplantation of organoid sheets from stem cells may be a promising approach/therapeutic for blinding diseases. Our data provide a proof-of concept for stem cell replacement mechanism and justify developing clinical therapies in RD patients with profound-to-total vision loss and fast-track FDA approval mechanism.

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**Poster**

**PSTR001. Differentiation and Reprogramming Stem Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR001.16/A16

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** NIH NS110586 (Conover)
Rudi Schulte Institute (Conover)

**Title:** Ventricular-subventricular zone analysis in a mouse model of post-infectious hydrocephalus

**Authors: *J. HERMAN**[1], N. RITTENHOUSE[3], A. MEZGER[1], A. KUMP[3], Y. WANG[2], F. MANDINO[4], P. VERARDI[2], E. LAKE[4], J. C. CONOVER[3];
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**Abstract:** Congenital hydrocephalus, a common birth defect affecting 1 in 770 infants, is characterized by expansion of the cerebroventricular system. One common cause of this disorder is infection, resulting in post-infectious hydrocephalus (PIH). We have developed a novel mouse model of PIH to analyze associated effects on the stem cell niche, the ventricle-subventricular zone (V-SVZ), located along the lateral wall of the lateral ventricles.
V-SVZ stem cells generate new neurons and glia during embryonic and postnatal development. To determine how these populations are affected during the course of PIH, we performed unilateral, intraventricular injections of influenza or its non-virulent component neuraminidase (using heat-inactivated influenza and saline as controls) at two timepoints, embryonic day 16 (E16) and postnatal day 4 (P4). Time points were chosen based on the changing composition of the ventricle wall. At E16, radial glia/stem cells together with some immature ependymal cells line the ventricle surface, thus exposing stem cells to direct infection. However, by P4, an ependymal cell monolayer is present with the stem cells relegated to the subependymal layer and retaining only a thin process in contact with the ventricle surface.
At E16, intraventricular injections of neuraminidase had no effect; mice did not develop hydrocephalus, and the ependyma was intact. However, injections of neuraminidase at P4 induced hydrocephalus in 58% of the mice based on MRI (11.7T) at P26-29. Ventricle expansion

was restricted to specific regions and ependymal denudation and astrogliosis were found exclusively associated with the expanded regions.
Intraventricular injection of influenza in E16 mice resulted in hypoxia with multiorgan vascular perturbations in all cases, even at a 100-fold dilution. For P4 mice, intraventricular injection of influenza resulted in a 76% hydrocephalus rate and unlike the neuraminidase cases (P4) which resulted in regional expansion, influenza injected mice developed global ventricle expansion. Surprisingly, the ventricle surface showed only limited ependymal denudation and astrogliosis. To determine stem cell output, we administered the thymidine analog EdU at P7, 3-days post-injection, and then analyzed whole mounts of the lateral ventricle at P30. We found an increased number of $EdU^+$ ependymal cells bordering regions of gliosis. Additionally, stem cell numbers and neurogenesis were assessed. Our studies demonstrate that while neuraminidase and influenza both result in hydrocephalus at P4, mice injected with influenza show that stem cell-mediated ependymogenesis can occur.

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**Poster**

**PSTR001. Differentiation and Reprogramming Stem Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR001.17/A17

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** NIH Grant R01DC018516

**Title:** Quantifying functional recovery of olfactory sensory neuron input to the olfactory bulb after methimazole treatment

**Authors: *K. CURTIS**[1], T. KUNKHYEN[2], C. E. CHEETHAM[2];
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**Abstract:** Olfactory sensory neurons (OSNs) are generated from basal stem cells in the olfactory epithelium (OE) throughout life in mammals. However, the specialized subset of navigator OSNs, which help ensure accurate axonal targeting, are only present during the perinatal period. Despite this, several studies have demonstrated some degree of recovery of olfactory bulb (OB) innervation and/or odor-guided behavior after injury or methimazole (MMZ)-mediated OSN ablation. Here, we investigated the extent of functional regeneration of glomerular maps in adult mice, which lack navigator OSNs. We used chronic, weekly in vivo 2-photon imaging following cranial window implantation in OMP-GCaMP6s mice to track odor responses of OSN axons in the OB, before and after MMZ-mediated OSN ablation. We analyzed odor-evoked responses either at the level of individual glomeruli, or using an unbiased grid-based approach, which enabled us to detect odor-evoked responses in any location within the imaged region. Grid-based analysis showed that baseline odor-evoked activity (percentage of grid squares showing ethyl

butyrate-evoked activity) was similar in mice that then received either MMZ (n = 4, median 71%) or saline as a control (n = 3, median 69%, p = 0.49, Mann-Whitney rank sum test). One week after MMZ treatment, odor-evoked activity was completely absent, confirming successful OSN ablation. Five weeks after MMZ or saline injection, odor-evoked activity remained significantly lower in MMZ-treated mice (10% of grid squares) compared to saline-injected controls (52% of grid squares, p = 0.003, Mann-Whitney rank sum test). This suggests that despite the OE having the requisite 5 weeks to repopulate with OSNs, regeneration of OSN input to the dorsal surface of the OB remains incomplete. Hence, OE repopulation is necessary but not sufficient for functional regeneration of OB input. Furthermore, together with previous studies, this suggests that partial regeneration of OSN input may be sufficient to mediate odor-guided behaviors.

**Disclosures: K. Curtis:** None. **T. Kunkhyen:** None. **C.E. Cheetham:** None.

**Poster**

**PSTR001. Differentiation and Reprogramming Stem Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR001.18/A18

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** NIH Grant R21EY030727

**Title:** Longitudinal monitoring of human cortical organoids implanted in adult mouse cortex with GCaMP6 and graphene electrode arrays

**Authors: *K. HERREMA**[1], E. MARTIN[1], M. WILSON[2], F. PUPPO[3], R. BLANCH GARCIA[4], A. MANSOUR[5,6], F. GAGE[5], T. O'SHEA[1], A. MUOTRI[3], D. KUZUM[2], A. DEVOR[1,7], M. THUNEMANN[1];
[1]Biomed. Engin., Boston Univ., Boston, MA; [2]Electrical and Computer Engin., [3]Pediatrics and Rady Children's Hospital, Cell. and Mol. Med., Univ. of California San Diego, La Jolla, CA; [4]Ctr. de Biotecnologia, Univ. Autonoma de Barcelona, Barcelona, Spain; [5]Salk Inst., La Jolla, CA; [6]Dept. of Med. Neurobio., The Hebrew Univ. of Jerusalem, Ein Kerem-Jerusalem, Israel; [7]Athinoula A. Martinos Ctr. for Biomed. Imaging, Dept. of Radiology, Harvard Med. School, Massachusetts Gen. Hosp., Charlestown, MA

**Abstract:** Human cortical organoids hold great potential as tools for disease modeling, personalized medicine, tissue regeneration, and more. However, inadequate oxygen supply leads to necrosis in the organoid core during extended *in vitro* culture limiting their maturation. Previous work by us and others demonstrated that implanting human cortical organoids into rodent brain leads to xenograft vascularization, and facilitates development and maturation of human neurons (Wilson, Thunemann, et al. 2022). We previously demonstrated integration of implanted cortical organoids using electrophysiological recordings with transparent graphene electrode arrays, structural two-photon imaging, and post-mortem immunostaining (Wilson,

Thunemann, et al. 2022). Combined with optical probes of neuronal activity, this approach can be used to measure activity of individual human neurons integrated into the mouse brain. Here, we used recombinant AAV with 7m8 serotype to transduce cultured organoids with a construct for GCaMP6s expression under control of the human synapsin promoter. After implantation into the retrosplenial cortex of adult immunodeficient mice, we observed GCaMP6s labeling of human neurons. We implanted GCaMP-labeled organoids into the mouse brain and performed longitudinal two-photon calcium imaging for up to 280 days after implantation. In parallel, we performed electrical recordings with transparent graphene electrode arrays. We observed changes in GCaMP6s fluorescence of individual cells synchronized with electrical activity measured from nearby electrodes. Over time, we observed a gradual shift in the activity pattern from low frequency, synchronous surges characteristic of an early fetal developmental stage to higher frequency, desynchronized events, consistent with neuronal maturation and network formation. In the future, we plan to extend this approach to patient-derived organoids and develop synthetic biomaterials to direct spatial patterning and maturation of the xenograft.

**Disclosures:** **K. Herrema:** None. **E. Martin:** None. **M. Wilson:** None. **F. Puppo:** None. **R. Blanch Garcia:** None. **A. Mansour:** None. **F. Gage:** None. **T. O'Shea:** None. **A. Muotri:** None. **D. Kuzum:** None. **A. Devor:** None. **M. Thunemann:** None.

**Poster**

**PSTR001. Differentiation and Reprogramming Stem Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR001.19/A19

**Topic:** A.03. Stem Cells and Reprogramming

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**Title:** Analysis of Secreted Profiles in Olfactory Epithelium Neuronal Progenitors Across Two Age Groups

**Authors: *O. LORA-MARIN**, L. GOMEZ-VIRGILIO, M. SILVA-LUCERO, M. CARDENAS-AGUAYO;
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**Abstract: Introduction.** Stem cells (SC) are cells with the capacity for self-renewal and multipotency. The immediate progeny of SCs are progenitor cells. These cells are found in the adult brain, which allows the formation of new neurons. On the other hand, olfactory sensory neurons require constant replacement from olfactory progenitor cells located in the olfactory epithelium. Regarding the release of soluble molecules, one way to determine which molecules are released in response to a stimulus received by a certain type of cell is through the analysis of

conditioned media (CM). Finally, previous studies show that there is a difference between molecules released in cells from young subjects compared to middle-aged adult subjects and their effect on progenitor cells of neural lineage. **Goals.** To determine the release profile of soluble factors obtained from conditioned media from progenitor cells of the olfactory epithelium isolated from subjects of two age groups. **Methods**. Obtaining and characterizing the precursor cells of the olfactory epithelium by immunodetection, BrdU incorporation, and determination of the population doubling time. Identification of soluble factors by immunodetection (Antibody array). **Results**. Progenitor cells of the olfactory epithelium expressed characteristic markers (SOX-2, Ki67, Nestin), of the progenitor and neuronal stage in both age groups. We found differential profiles of soluble factors between the two age groups, being less soluble factors secreted in the middle-aged group as compared to the young group. **Conclusions.** Differential expression profiles in soluble factors from subjects of different ages could be key when choosing a possible cell-free therapy for CNS pathologies

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**Poster**

**PSTR001. Differentiation and Reprogramming Stem Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR001.20/A20

**Topic:** A.03. Stem Cells and Reprogramming

**Title:** Functional profile of neural networks with different ratios of inhibitory and excitatory neurons

**Authors: *E. CROCCO**, F. TONELLI, G. GHILONI, F. CANCELLOTTI, F. CREMISI; Scuola Normale Superiore - Pisa, Pisa, Italy

**Abstract: INTRODUCTION**: To make a working nervous system, two forces are necessary: excitation andinhibition. The impact of different ratios of GABAergic neurons on the functioning of local corticalnetworks is so far not completely known. In recent years mouse embryonic stem cells (mESCs) havebeen used as a promising tool for an in vitro recapitulation of many differentiation processes thatoccur during neurogenesis and neural development. So, it is possible to generate cultures withglutamatergic or GABAergic neurons.**AIM**: We aim to have a functional characterization of cortical cell cultures with different ratios ofinhibitory and excitatory neurons, with the purpose of observing neuronal differentiation, synapticformation, and neural activity by the use of intracellular $Ca^{2+}$ live imaging, optogenetic andelectrophysiological tools (MEA).**METHODS:** The achievement of this goal was validated by qRT-PCR, immunocytodetection,calcium imaging experiments and electrophysiological analysis.**RESULTS**: With the use of Cyclopamine and SAG (Smoothened Agonist), we established newprotocols to create distinct cultures of excitatory and inhibitory neurons, observing cortical andstriatal gene markers, such as Pax6, Nkx2.1, Dlx1, Lhx8. We found 94%

of vGlut2 positive neuronsand 80% of GAD65 and Parvalbumin positive neurons, respectively. We designed cortical cellpopulations with different E/I (excitation/inhibition) ratios, developing a physiological (80/20) andan experimental condition (50/50). By lentiviral transduction, we created a polyclonal cell line thatexpresses GcaMP6s, a genetically encoded calcium indicator, and we performed longitudinal calciumimaging to infer frequency and synchronization of neural activity. Preliminary results may providevaluable hints and a multidimensional profile for network activity, the single-neuron frequency andthe index of synchronization of these cultures.**CONCLUSIONS**: The setup of an *in vitro* model of cortical network could be useful to functionallystudy the activity and plasticity of cortical inhibitory networks and could help to comprehend diseasessuch as autism or schizophrenia.

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**Poster**

**PSTR001. Differentiation and Reprogramming Stem Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR001.21/A21

**Topic:** A.03. Stem Cells and Reprogramming

**Title:** The role of transcription factor NR2E1 in NSC maintenance and differentiation

**Authors: *D. SEO**, F. R. SANTORI, N. B. IVANOVA;
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**Abstract:** Neurodevelopmental disorders lead to disability or death, thus exerting a substantial burden on society. Neurodevelopmental disorders are often associated with disruptions of precisely coordinated events during brain development. During early brain development, the neural stem cell (NSC) pool is maintained through proliferation (a process known as self-renewal) to generate the correct numbers of neurons, astrocytes, and oligodendrocytes. NR2E1 is a transcription factor known to play a role in NSC self-renewal in mice. In humans, mis-regulation of NR2E1 is associated with schizophrenia, bipolar disorder, and aggression. However, it is unclear how NR2E1 affects human brain development. To investigate the role of NR2E1 in NSC maintenance in humans, we have generated NR2E1-knockout (NR2E1-KO) human embryonic stem cells (hESCs) using CRISPR-Cas9. We differentiated NR2E1-KO and wild-type (WT) hESCs into NSCs and performed neurosphere assays to assess self-renewal. We observed a reduction in the number and size of neurospheres from NR2E1-KO NSCs compared to neurospheres from WT NSCs (8 experiments, Student's t test, $p<0.0001$). These results suggest that NR2E1 is required for self-renewal of human NSCs. Bulk RNA sequencing and immunofluorescence analyses of NR2E1-KO and WT neural rosettes revealed a possible role for NR2E1 in the extracellular matrix organization of NSC niches, which could contribute to NSC maintenance. To study the impact of NR2E1 on NSC differentiation into neuronal and glial cells, we generated cortical organoids from NR2E1-KO and WT ESCs. NR2E1-KO organoids were

significantly smaller compared to WT from the early stage of organoid development (2 experiments with 24 organoids per group, unpaired t test, $p<0.0001$). We performed quantitative PCR (qPCR) analyses using marker genes specific for different cell types present within the organoids. Marker genes for cell proliferation and upper layer neurons were downregulated, while marker genes for GABAergic neurons and early glial cells were upregulated in NR2E1-KO organoids compared to WT organoids (2 experiments with 24 organoids per group, unpaired t test, $p<0.0001$). For cell type identification and molecular characterization of individual cells, we are conducting a time course single cell RNA-sequencing on NR2E1-KO and WT organoids. Our findings suggest that NR2E1 is required for NSC pool maintenance as well as the differentiation of NSCs to neuronal and glial cells during the initial phases of human brain development. This work will reveal the mechanisms of neurodevelopmental disorders arising from the defect in NSC functions.

**Disclosures: D. Seo:** None. **F.R. Santori:** None. **N.B. Ivanova:** None.

**Poster**

**PSTR001. Differentiation and Reprogramming Stem Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR001.22/A22

**Topic:** A.03. Stem Cells and Reprogramming

**Support:** Scottish Rite Charitable Foundation of Canada
Brain Canada Foundation
CFI Grant 037755

**Title:** Investigating the impact of delta-9-tetrahydrocannabinol (THC) on GFAP expression in health and schizophrenia with human organoid models of brain development

**Authors:** B. ALURAL[1], L. REYNOLDS[1], B. BALL[1], J. GEDDES-MCALISTER[1], J. KHOKHAR[2], S. D. SHERIDAN[3], R. H. PERLIS[3], M. ALPAUGH[1], ***J. LALONDE**[1];
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**Abstract:** Studies of cannabis use in teenagers have suggested that repeated exposure can modify cognitive development and puts users at heightened risk of developing psychiatric disorders, including schizophrenia (SZ). However, current research into the mechanisms behind these associations have been hampered by the necessity of using non-human models to study cerebral cortex formation at the cellular and molecular levels. To address this gap, we differentiated induced pluripotent stem cells (iPSCs) into 3-dimensional (3D) brain organoids and evaluated proteome differences between specimens produced from controls and patients with SZ with and without delta-9-tetrahydrocannabinol (THC) application to the maturation media. Our mass spectrometry (MS)-based proteomics analysis testing THC's effect on early brain development demonstrated that organoids prepared from SZ patients had significantly lower

levels of Glial fibrillary acidic protein (GFAP) than those from control individuals. Most interestingly, we also discovered that THC added to the culture of 125-days-old control organoids (chronic condition, 50 nM for the last 10 days) resulted in lower GFAP level. Together, these results suggest a connection between the expression of GFAP and cannabinoid signaling on one hand, and the possible contribution of aberrant GFAP levels to SZ on the other. Here, we present the characterization of the 6 hiPSC lines (3 SCZ patients and 3 healthy control individuals) used in our study. Second, we report the completed quantitative MS analysis of our 6 iPSCs lines matured for 125 days as organoids where we identified 37 proteins, including GFAP, with significant differences in abundance between healthy control and SCZ specimens or resulting from THC application to the maturation culture media. Finally, we highlight ongoing imaging efforts at describing the specific GFAP-expressing cell types in unguided brain organoid models that are affected by THC, as well as related experiments done with our control and SZ iPSC lines differentiated in a monolayer fashion as astrocytes that explore the growth, maturation, and activity of these cells. Together, our efforts provide new insights about the impact of THC on cells expressing GFAP during prenatal stages of cerebral cortex development, as well as possible connections to the pathogenesis of SZ.

**Disclosures: B. Alural:** None. **L. Reynolds:** None. **B. Ball:** None. **J. Geddes-McAlister:** None. **J. Khokhar:** None. **S.D. Sheridan:** None. **R.H. Perlis:** None. **M. Alpaugh:** None. **J. Lalonde:** None.

**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.01/A23

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

**Support:** NINDS IRTA

**Title:** Type III Neuregulin-1 back-signaling regulates axonal mitochondrial dynamics in developing ventral hippocampal neurons

**Authors: *K. C. HOSPES**[1], D. FREEMAN[2], L. W. ROLE[3], D. A. TALMAGE[3];
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**Abstract:** Type III Neuregulin-1 (NRG1) is a transmembrane, bidirectional signaling molecule that regulates multiple aspects of neuronal development, including axonal outgrowth, synapse formation, and maturation. Axonal Type III NRG1 “back” signaling, activated by binding to ErbB4, regulates pre-synaptic release sites. Regulation of mitochondrial dynamics is necessary to maintain neuronal homeostasis, especially at presynaptic terminals. In this study, we asked whether Type III NRG1 signaling affects mitochondrial dynamics in axons of ventral hippocampal neurons, focusing on this region because of its importance in learning, memory,

motivation, and in cognitive disorders like schizophrenia, for which NRG1 is a candidate gene. To examine possible effects of Type III NRG1 signaling on mitochondrial motility, we labeled mitochondria of P0 ventral hippocampal primary cell cultures with Mitotracker at DIV7. We measured movement patterns by live imaging before and after stimulation with ErbB4. Overall, stimulating NRG1 signaling reduced motility, with about 25% of dynamic mitochondria becoming stationary. We then fixed our cultures at various time points of ErbB4 stimulation and stained with antibodies recognizing Type III NRG1. These studies revealed that ErbB4 treatment increased colocalization between Type III NRG1 and mitochondria, consistent with our hypothesis of NRG1 signaling recruiting dynamic mitochondria. Next, we quantified mitochondrial volume and density in stimulated axons. We measured mitochondrial volume using Feret's diameter and defined density as the number of mitochondria per unit axonal area. Mitochondrial volume transiently increased, peaking at 1-hour post-ErbB4 stimulation, and returning to baseline after 4 hours. Mitochondrial density transiently decreased before returning to pre-stimulation levels. During live imaging, we also observed changes in the number of mitochondrial fusion and fission events after ErbB4 stimulation. Ongoing experiments are probing the mechanisms by which NRG1 signals to mitochondria. We are measuring changes in mitochondrial motility and morphology in the presence of pharmacological inhibitors of the PI3K and ERK pathways (inhibitors include Wortmannin and U0126, respectively). Ultimately, we found that NRG1 signaling affects axonal mitochondrial movement and morphology in the ventral hippocampus, potentially implicating the fusion-fission balance or various signaling cascades that may be important for neuronal development, homeostasis, and transmission.

**Disclosures: K.C. Hospes:** None. **D. Freeman:** None. **L.W. Role:** None. **D.A. Talmage:** None.

**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.02/B1

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

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

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

**Authors: *L. JIANG**, M. ANANTH, L. BAI, L. W. ROLE, D. A. TALMAGE;
NIH/ NINDS, Bethesda, MD

**Abstract:** Type III Neuregulin 1 (Nrg1) is important for neuronal development and function. Our earlier studies have shown Nrg1 signaling is required for cholinergic modulation of excitatory plasticity at cortical-BLA synapses and activation of cholinergic input from basal forebrain can enhance fear learning. However, the role of Nrg1 signaling in cholinergic

modulation of fear-learning is not clear. We are using a mouse model with a psychosis-related Nrg1 mutation that impairs γ-secretase-mediated nuclear signaling, to investigate the contribution of Nrg1 signaling to cholinergic innervation of the BLA. We crossed the Nrg1 mouse line with a Chat-TauGFP transgenic line in which cholinergic neurons and their projections are fluorescently labeled. Using these animals we are studying the basal forebrain cholinergic neurons in the nucleus basalis of Meynert (NBM) and cholinergic innervation to BLA from the second post-natal week through young adulthood (~PND15 - PND45). In wild type animals cholinergic neurons are present in the NBM by PND17. No cholinergic innervation of the BLA is seen at this point. At PND28 the BLA is highly innervated with cholinergic axons. We are currently refining the timing of cholinergic innervation of the BLA and examining the effect of reduced Nrg1 signaling on this process at this point. To complement these morphological studies, we are using optogenetic techniques to examine the effect of decreased Nrg1 signaling on the maturation of synaptic plasticity and cholinergic modulation of glutamatergic synapses from anterior cingulate cortex to BLA principal neurons. Our current study is helping to understand how Nrg1 local and nuclear back signaling contributes to development and cholinergic modulation of fear learning related circuits.

**Disclosures:** **L. Jiang:** None. **M. Ananth:** None. **L. Bai:** None. **L.W. Role:** None. **D.A. Talmage:** None.

**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.03/B2

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

**Support:** Supported by NIH Intramural Program

**Title:** Reductions in Type III Neuregulin-1 affect basal forebrain cholinergic neurons during development

**Authors: *T. E. MUIR**, M. R. ANANTH, L. W. ROLE, D. A. TALMAGE;
NINDS/NIH, Bethesda, MD

**Abstract:** Neuregulin-1 (Nrg1), a component of the epidermal growth factor family, is critical for neuronal differentiation, migration, and survival. Of the many Nrg1 isoforms, the cystine rich domain (CRD) Type III Nrg1 is unique not only in its structure, but in its potential for juxtacrine, bidirectional signaling: forward signaling via its ErbB receptor partner, and back-signaling into the Type III Nrg1-expressing cell. Studies using Type III $Nrg1^{-/-}$ mice have found it plays a critical role in synapse formation and maintenance as well as neuronal survival. Specifically, we have found that TrkA+ sensory neurons of the peripheral nervous system show reduced survival and abnormal pathfinding in Type III $Nrg1^{-/-}$ mice. In the central nervous system, basal forebrain cholinergic neurons (BFCNs) express TrkA, and their targets express its signaling partner, nerve

growth factor (NGF). Together, NGF/TrkA signaling is crucial for normal development of BFCNs. We hypothesized that reductions in Type III Nrg1 could lead to reduced survival of TrkA+ BFCNs and impaired target innervation. These reductions in Type III Nrg1 would lead to long-term circuit vulnerability in BFCNs across lifespan. To test this, we first evaluated the density of BFCNs in young, 2.5 month old, WT and mice with heterozygous disruption of the Type III Nrg1 gene (CRD-HT). Preliminary data revealed fewer Chat+ neurons in the posterior basal forebrain (NBM/SI) as compared to WT mice. Next, we asked whether this deficit in cholinergic neuron number resulted in impaired innervation of target regions. Preliminary findings showed fewer cholinergic terminals in the BLA of CRD-HT as compared to WT animals. Finally, we asked whether this population of BFCNs in CRD-HT mice experienced abnormal, accelerated deterioration with age compared to WT counterparts. Surprisingly, preliminary data showed an equivalent number of Chat+ cells in the NBM/SI in aged CRD-HT and WT mice. Early data support a role for Type III Nrg1 in BFCN development that is compensated overtime by other factors. Ongoing studies assess the developmental trajectory of BFCN development and the time-course of the normalization of Chat-expression in CRD-HT mice.

**Disclosures:** **T.E. Muir:** None. **M.R. Ananth:** None. **L.W. Role:** None. **D.A. Talmage:** None.

**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.04/B3

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

**Support:** NIH R37-HD081168
SRSF Career Development Award

**Title:** Developmental influence of M1 on the red nucleus in weanling rats

**Authors: *J. C. DOOLEY**[1], G. SOKOLOFF[2], M. S. BLUMBERG[3];
[1]Purdue Univ., West Lafayette, IN; [2]The Univ. of Iowa, Iowa City, IA; [3]Psychological and Brain Sci., Univ. of Iowa, Iowa City, IA

**Abstract:** The motor functions of primary motor cortex (M1) emerge quite late, with previous work in anesthetized rats suggesting that M1 is not capable of motor control until postnatal day (P) 25. However, the developing motor cortex is not silent: Throughout early infancy, neural activity in M1 reflects sensory feedback from moving limbs. Then, around P20, neural activity in M1 co-occurs with movement. Before M1 contributes to motor behavior, the limb movements of infant rats are produced by the red nucleus (RN). Although we have long known that M1 and the RN develop on different timelines, we know very little about how M1 influences activity in the RN before the onset of M1-mediated motor control. Here, to examine neural interactions between M1 and the RN, we injected a retrograde AAV (AAV-Syn-Chronos-GFP) into the RN

of developing rats, with the goal of expressing the opsin in RN-projecting neurons in M1. AAV injections were performed at P8, which is after M1 projections to the RN are established. We then wait 2 weeks for the virus to travel and be expressed in M1 cell bodies. At P22 to P24, rats were headfixed in the Mobile HomeCage, which allows unanesthetized rats at these ages to locomote and sleep. While recording extracellular activity in the RN, we optogenetically stimulated corticorubral neurons using an optrotrode in M1 as rats cycled between sleep and wake. M1 stimulation drove activity in both M1 and RN neurons. Interestingly, whereas optical stimulation affected M1 activity immediately, there was a significant lag in the effect on RN activity, suggesting that M1 is influencing the RN at these ages. Finally, during REM sleep, we observed a continuous and coherent theta oscillation in both M1 and the RN. When present, theta influenced how much activity resulted from optogenetic stimulation, with stimulation during trough of theta resulting in more neural activity, and stimulation during the peak of theta resulting in less neural activity. Current work is focusing on whether M1 stimulation influences movement, and whether the patterning of M1-RN interactions are influenced by sleep-wake states.

**Disclosures:** **J.C. Dooley:** None. **G. Sokoloff:** None. **M.S. Blumberg:** None.

**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.05/B4

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

**Support:** NIH Grant R00NS114166
Brain & Behavior Research Foundation Young Investigator Award GR114536
NIH Grant R01MH110553

**Title:** Early L5 to L2/3 connections drive spontaneous columnar activity in the barrel cortex

**Authors: J. VARGAS-ORTIZ**[1], V. MARTINEZ[1], R.-J. LIU[1], R. BABIJ[3], Z. S. DUAN[3], S. WACKS[3], S. KHAN[1], A. WANG[1], J. SOTO-VARGAS[1,2], N. DE MARCO GARCIA[3], *A. CHE[4,1];
[1]Dept. of Psychiatry, [2]Interdepartmental Neurosci. Program, Yale Univ. Sch. of Med., New Haven, CT; [3]Ctr. for Neurogenetics, Brain and Mind Res. Inst., Weill Cornell Med., New York, NY; [4]Yale university, new haven, CT

**Abstract:** Synchronous electrical activity is a hallmark of the developing CNS, playing critical roles in neuronal maturation and circuit refinement. In the mouse somatosensory cortex (S1), spontaneous neuronal activity (SNA) during the early postnatal stage is organized in columns and is required for sensory map formation. While thalamic inputs are thought to coordinate layer (L) 4 activity, the source of the robust L2/3 activity at this early stage is unknown. In addition,

there is still considerable debate on whether the columnar activation reflects smaller cortical columns consisting of neurons originated from the same radial glia lineage, or whether it is organized in barrel columns as early as the 1st postnatal week (PNW). Using a novel microprism preparation and *in vivo* 2-photon imaging in neonatal mice, we showed that SNA in S1 was synchronized translaminarly from deep to superficial layers and corresponded to functional barrel columns. To identify the source of L2/3 activation, we performed slice electrophysiology throughout the first three PNWs. We found that L2/3 pyramidal neurons received large L5 inputs but relatively weak L4 inputs during the 1st PNW. L4 to L2/3 inputs drastically increased in strengths from the 1st to the 3rd PNW, while L5 to L2/3 input strengths remained stable. Results from rabies transsynaptic tracing experiments support that L2/3 pyramidal neurons receive large number of presynaptic inputs from L5 during the 1st PNW, before the number of L4 presynaptic inputs increases as the canonical thalamocortical circuit matures. Preliminary data suggest silencing L5 synaptic outputs chemogenetically or by selectively expressing tetanus toxin light chain (TeLC) resulted in a reduction in L2/3 SNA in the 1st PNW, as well as abnormal L4-L2/3 connectivity and whisker-evoked activation in the 3rd PNW. Our results demonstrate that early SNA in S1 is organized in barrel columns and driven by L5 pyramidal neurons, and that strong, transient L5 to L2/3 inputs play a pivotal role in providing the activity required for the maturation of L2/3 pyramidal neurons and L4-L2/3 connection, thus supporting the formation of the columnar organization in the barrel cortex.

**Disclosures: J. Vargas-Ortiz:** None. **V. Martinez:** None. **R. Liu:** None. **R. Babij:** None. **Z.S. Duan:** None. **S. Wacks:** None. **S. Khan:** None. **A. Wang:** None. **J. Soto-Vargas:** None. **N. De Marco Garcia:** None. **A. Che:** 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.; Duraviva.

**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.06/B5

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

**Support:** University of Massachusetts Boston Grant PDG-21-13

**Title:** A timeline of hippocampal perineuronal net development in male vs female rats

**Authors: *A. WOJCIK**[1,2], S. L. ZUP[3,2];
[1]Univ. of Massachusetts, Boston, Malden, MA; [2]Developmental and Brain Sci., Univ. of Massachusetts Boston, Boston, MA; [3]Univ. Massachusetts, Boston, Univ. of Massachusetts, Boston Dept. of Psychology, Dorchester, MA

**Abstract:** Perineuronal nets (PNNs) are crucially important for neurodevelopment, however there is no sex-specific timeline as to how they develop or if they develop differently in males

and females. PNNs are unique non-neuronal structures in the brain that surround neurons, especially GABAergic, parvalbumin (PV) positive inhibitory interneurons. PNNs help regulate functions such as the formation and stabilization of synaptic connections and excitation/inhibition balance in the brain. Alterations in plasticity and excitation/inhibition imbalances have been linked to developmental disorders, making PNNs a relevant structure that may be associated with changes that occur in the brain when a neurodevelopmental disorder is present. In this study we used immunohistochemistry to label PNNs and determine a timeline of PNN development in juvenile Sprague Dawley rats aged postnatal day (p)14, p16, p18, and p22 in regions CA1, CA2, CA3 and the dentate gyrus (DG) of the hippocampus. These ages were chosen because PNNs have been found to begin to develop in the hippocampus around p14 and start to mature around p21, but exact ages and if those ages differ by sex, is unknown. We expected to see an approximate linear increase in the number of PNNs as age increased in both male and female rats, though we hypothesized that males would have more PNNs by p18 than females due to previous published work from our lab. Although the data are preliminary, there were significant main effects of age in regions CA3 and the DG, with PNNs increasing with age, as hypothesized. There was also a significant interaction between age and sex, surprisingly showing that females had more PNNs than males at p22 ($p<.001$) in both CA3 ($p = .001$) and DG ($p = .003$). Looking across the timeline, female rats exhibited a steady increase in PNN numbers with age, but male PNN numbers were more variable or even stayed constant as animals aged. This sex difference in the timeline of PNN development adds insight into the known sex difference seen in etiology of neurodevelopmental disorders associated with excitation/inhibition imbalances such as autism spectrum disorder (ASD), epilepsy, attention deficit hyperactivity disorder (ADHD) and schizophrenia.

**Disclosures:** **A. Wojcik:** None. **S.L. Zup:** None.

**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.07/B6

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

**Title:** Characterization of synaptic and neuronal maturation in models of neurodevelopmental disorders with altered of $GABA_A$ α5 receptor signaling

**Authors: *J. M. SCHULZ**[1], K. BEHR[1], E. A. KAPLANIAN[1], C. VILLEGAS DIAZ[1], T. TAKUMI[2], M.-C. HERNANDEZ[1];
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**Abstract:** Gene dosage of GABRA5 has been implicated in severe neurodevelopmental disorders including Angelman Syndrome (AS) and Dup15q syndrome. Both in humans and

rodents, GABRA5 is highly expressed in early postnatal development. $GABA_A$ α5 receptors have been shown to promote dendrito- and synaptogenesis. Recently, a monoallelic de novo missense variant in GABRA5 resulting in a V294L amino acid change was identified in patients with severe early-onset epilepsy (EOE). Importantly, the GABRA5 p.V294L variant was 10-times more sensitive to GABA indicating that the underlying cause is a gain of function of the receptor. How a gain-of-function mutation that is expected to result in increased GABAergic signaling causes severe EOE is unclear at present. Here, we investigated the development of L2/3 pyramidal neurons in the somatosensory cortex from a mouse model harboring the point mutation found in EOE patients, $Gabra5^{+/V294L}$, and compared it to a mouse line with a heterozygous deletion of a gene cluster encoding the α5, β3, and γ3 subunits of GABAA receptors commonly found in AS, $Gabr^{+/-g3a5b3}$. We used patch-clamp electrophysiology in brain slices and combined it with immunohistochemistry of biocytin-filled neurons, confocal microscopy and molecular biology. Parietal cortex of $Gabra5^{+/V294L}$ mice had normal expressions of Gabra5 mRNA, while $Gabr^{+/-g3a5b3}$ mice showed the expected reduction of Gabra5, Gabrg3, Gabrb3 mRNA. L2/3 pyramidal neurons of $Gabra5^{+/V294L}$ mice showed increased responses to bath application of isoguvacine supporting a gain of function of the GABAA α5 receptors. Analysis of miniature IPSCs showed a faster decay time constant in $Gabr^{+/-g3a5b3}$ mice at P8 confirming the decreased contribution of $GABA_A$ α5 receptors to synaptic transmission in early development. However, there were no major changes of the other parameters across development. In contrast, there was a pronounced upregulation of mEPSC frequency in $Gabra5^{+/V294L}$ mice, which was paralleled by increased spine density on the morphological level. These preliminary results indicate that a gain of function mutation of $GABA_A$ α5 receptors can cause profound changes of both GABAergic and glutamatergic inputs, and may have important implications for defining an optimal temporal treatment window in the related disorders.

**Disclosures:** **J.M. Schulz:** A. Employment/Salary (full or part-time); Pharma Research & Early Development, F. Hoffmann-La Roche Ltd, Basel, Switzerland. **K. Behr:** A. Employment/Salary (full or part-time); Pharma Research & Early Development, F. Hoffmann-La Roche Ltd, Basel, Switzerland. **E.A. Kaplanian:** A. Employment/Salary (full or part-time); Pharma Research & Early Development, F. Hoffmann-La Roche Ltd, Basel, Switzerland. **C. Villegas diaz:** A. Employment/Salary (full or part-time); Pharma Research & Early Development, F. Hoffmann-La Roche Ltd, Basel, Switzerland. **T. Takumi:** 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.; Dpt.Physiol. & Cell Biol., Kobe Univ. Sch. Med., Chuo, Kobe, Japan. **M. Hernandez:** A. Employment/Salary (full or part-time); Pharma Research & Early Development, F. Hoffmann-La Roche Ltd, Basel, Switzerland.

**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.08/B7

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

**Support:** NIMH R01 MH124695-01

**Title:** Striatum regulates the postnatal maturation of GABAergic connectivity of prefrontal cortical circuits.

**Authors: *M. JANECEK**, Y.-C. SHIH, R. PEIXOTO;
Univ. of Pittsburgh, Pittsburgh, PA

**Abstract:** Prefrontal cortex (PFC) and the basal ganglia are interconnected through a series of cortico-striato-thalamo-cortical (CSTC) loops that are critical for higher-order cognitive and motor functions, and whose dysfunction is implicated in multiple neurodevelopmental disorders. Whereas the role of cortical activity in regulating striatal development is well established, how striatal activity shapes the maturation of upstream cortical circuits remains unknown. Striatal spiny projection neurons (SPNs) expressing dopamine 1 receptor (D1-SPNs) and dopamine 2 receptor (D2-SPNs) play opposing roles in regulating the activity of CSTC loops. Our previous work has shown that unilateral focal ablation of D1-SPNs reduces by postnatal day 14 (P14) population activity in upstream PFC regions that innervate manipulated striatal regions. By contrast, D2-SPN ablation causes the opposite phenotype resulting in cortical hyperactivity. Together, these experiments demonstrate that striatal circuits already modulate cortical activity during postnatal development. Here we further characterized how unilateral focal ablation of striatal D1- or D2-SPNs alters the developmental trajectory of PFC connectivity. At P14-15, we intracellularly recorded excitatory and inhibitory miniature postsynaptic currents (mPSCs) onto L2/3 pyramidal neurons (PNs) in the hemisphere neonatally injected with a Cre-dependent caspase-3. D2-SPN ablation in A2A $Cre^+$ pups did not affect the frequency of mEPSC onto PNs in PFC, but it decreased GABAergic connectivity onto PNs 1.5-fold. In contrast, D1-SPN ablation in D1-$Cre^+$ pups increased inhibitory mPSC connectivity 1.4-fold. These distinct connectivity effects extend our previous population-level findings and, taken together, indicate that imbalanced striatal output affects the establishment of prefrontal inhibitory GABAergic connectivity at P14-15.

**Disclosures:** **M. Janecek:** None. **Y. Shih:** None. **R. Peixoto:** None.

**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.09/B8

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

**Support:** NSF 1943514
NIH NS117686

**Title:** Hyperglycaemic culture conditions for rodent primary neurons creates a metabolic environment different to that in vivo

**Authors: D. M. ROBERTS**[1], *S. SWAIN[1], S. CHOWDHRY[2], R. B. RENDEN[3];
[1]Physiol. and cell Biol., Univ. of Nevada, Reno, Reno, NV; [2]Physiol. and cell Biol., Univ. of Nevada, Reno, Las Vegas, NV; [3]Physiol. and cell Biol., Univ. of Nevada, Reno Sch. of Med., Reno, NV

**Abstract:** Among the many factors involved in maintaining rodent primary neuronal cultures, the media we use to culture them is one of the most important. The standard modern approach to primary neuronal culture grows neurons in a high glucose environment, in media containing ~25mM glucose. This hyperglycaemic condition is much higher than the *in vivo* concentration of glucose (1 to 2.5 mM) found in the interstitial spaces of the human brain. We were curious to see if hyperglycaemic culture conditions affect the balance of ATP maintenance produced by glycolysis and mitochondrial respiration in cultured neurons, relative to neurons grown in more physiological glucose conditions. We grew relatively pure neuronal cultures, with <10% glial contamination, from neonatal C57bl6 mice for 14 days in commercially available media (Thermofisher Neurobasal Plus, 25 mM Glucose) and media (Thermofisher Neurobasal A, No Glucose) with 5 mM glucose added. We found neurons grew healthily in both glucose concentrations until at least 14 days in vitro, forming synapses, and exhibiting network activity. When testing for ATP levels using a luciferin luminescence assay, we found neurons grown in 25 mM glucose opted to use glycolysis as their primary pathway for ATP, with minor production of ATP by mitochondrial oxidative phosphorylation (OxPhos). Neurons grown in 5 mM glucose showed a more balanced dependence on glycolysis and OxPhos. This report shows that neurons cultured in high glucose media are predisposed to use glycolysis over OxPhos. This finding stands in opposition to what is known for in vivo neurons which are more dependent on OxPhos as the primary pathway for ATP maintenance. Our work challenges the validity of using standard primary neuronal culture systems to represent physiologically relevant neuronal respiration and suggests previous studies on neuronal metabolism in primary neuronal cultures may require critical review.

**Disclosures: D.M. Roberts:** None. **S. Swain:** None. **S. Chowdhry:** None. **R.B. Renden:** None.

**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.10/B9

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

**Support:** Wellcome Trust

**Title:** The maturation of parvalbumin interneurons is controlled by the activity-dependent expression of PGC-1α

**Authors: *M. MOISSIDIS**[1], L. ABBASOVA[1], C. BERNARD[1], A. KELLY[2], S. QIN[1], F. OOZEER[1], P. LAVENDER[2], N. FLAMES[3], O. MARIN[1];
[1]Ctr. for Developmental Neurobio., [2]Peter Gorer Dept. of Immunobiology, King's Col. London, London, United Kingdom; [3]Neurobiologia del Desarrollo, Insituto De Biomedicina De Valencia CSIC, Valencia, Spain

**Abstract:** Parvalbumin (PV) interneurons represent the most abundant subclass of cortical interneurons and are essential for gating and pacing the activity of excitatory neurons. PV interneurons have a very protracted development and only begin acquiring their mature properties toward the end of the second postnatal week in mice. Cortical activity is thought to regulate the maturation of PV interneurons, but the molecular mechanisms through which this is achieved remain poorly understood. Using chemogenetic tools that modulate the excitability of prospective PV interneurons, as well as interfering with glutamate release and the formation of excitatory synapses contacting PV interneurons, we found that the maturation of these cells is modulated by neuronal activity. This process requires PGC-1α (peroxisome proliferator activated receptor-gamma coactivator 1 alpha), a transcriptional co-modulator upregulated by PV interneurons towards the end of the first week of postnatal development. Developmental loss of PGC-1α prevents the maturation of PV interneurons, which fail to express many characteristic markers of adult PV cells. Single-cell RNA-sequencing analysis of conditional PGC-1α mutants revealed broad transcriptional changes across multiple cellular domains, suggesting that this factor is a master regulator of the terminal differentiation of PV interneurons. Overall, our results indicate that PGC-1α functions as a molecular switch that translates neural activity into transcriptional programmes promoting the maturation of PV interneurons.

**Disclosures: M. Moissidis:** None. **L. Abbasova:** None. **C. Bernard:** None. **A. Kelly:** None. **S. Qin:** None. **F. Oozeer:** None. **P. Lavender:** None. **N. Flames:** None. **O. Marin:** None.

**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.11/B10

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

**Support:** Klingenstein Fund
Simons Foundation
NINDS K12 Neurosurgery Research Career Development AwardNIH K-12 award

**Title:** Network-wide remodeling following interneuron precursor transplantation reduces seizures in an in vitro organotypic model

**Authors: *E. A. MATTHEWS**[1], M. D. ADOFF[1], M. YEO[1], M. METHANI[1], P. THOMPSON[1], D. G. SOUTHWELL[2];
[1]Dept. of Neurosurg., [2]Neurosurg. and Neurobio., Duke Univ., Durham, NC

**Abstract:** In rodent models of epilepsy, transplanted interneuron precursors incorporate into recipient cortical areas, increase synaptic inhibitory signaling events, and reduce seizures (*1*, *2*). The mechanisms by which transplants improve seizure phenotypes are not fully understood, but one plausible hypothesis is that interneuron transplantation counteracts epileptogenic hyperexcitability by increasing synaptic inhibition onto recipient neurons. However, in some *in vivo* models, transplantation has also been associated with increases in recipient synaptic excitation (*3*), which perhaps results from homeostatic processes that engage in the recipient. It remains unknown whether transplants must increase net inhibition in order to suppress seizures, or if they can improve seizure phenotypes without shifting recipient inhibitory-excitatory balance. Here we used wild type organotypic hippocampal slice cultures (OHSCs), a model of epileptogenesis that generates spontaneous seizure-like activity, to evaluate how transplantation alters key determinants of synaptic inhibition and excitation in the context of seizure correction. As in in vivo epilepsy models, transplanted interneuron precursors migrated, survived, and differentiated into mature interneurons in OHSCs. Transplants also increased inhibitory signaling onto slice neurons and corrected slice seizure phenotypes. Surprisingly, while transplantation increased synaptic inhibition onto recipient slice cells, it did not change recipient cellular inhibitory-excitatory balance. Additionally, we found that measures of synaptic excitation, including miniature excitatory postsynaptic currents, were increased in both excitatory and inhibitory cell populations of the OHSCs. Moreover, slice excitatory and inhibitory populations also exhibited increased excitability in the transplant condition. Altogether, our results indicate that, rather than simply boosting inhibition in epileptogenic circuits, interneuron transplantation may drive more widespread changes in recipient inhibitory and excitatory synaptic connectivity, as well as recipient cellular excitability. Our findings furthermore provide evidence that interneuron transplantation can correct seizure activity without altering or correcting inhibitory-excitatory balance. 1. S. C. Harward, D. G. Southwell *Neurosurg. Focus*. **48**, E18 (2020). 2. B. Zhu, J. Eom, R. F. Hunt *Nat. Commun.* **10**, 5156 (2019). 3. M. A. Howard, J. L. R. Rubenstein, S. C. Baraban *Proc. Natl. Acad. Sci. U. S. A.* **111**, 492–497 (2014).

**Disclosures: E.A. Matthews:** None. **M.D. Adoff:** None. **M. Yeo:** None. **M. Methani:** None. **P. Thompson:** None. **D.G. Southwell:** None.

**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.12/B11

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

**Support:** NIH IPR Grant ZIAMH002959

**Title:** Development of cortical disinhibitory circuits

**Authors: *S. LEE**, A. INACIO, P. STEVENSON, J. QI, S. NASKAR;
NIH, Natl. Inst. of Mental Hlth. (NIMH), Bethesda, MD

**Abstract:** Disinhibition mediated by vasoactive intestinal polypeptide (VIP)-positive GABAergic interneurons (INs) is a robust circuit motif found in multiple cortical areas. VIP INs inhibit other types of cortical GABAergic INs, but its inhibition of dendrite-targeting somatostatin (SST)-positive INs is particularly strong, leading to the disinhibition of pyramidal neurons. This cortical disinhibitory circuit motif has been shown to play an important role in sensorimotor integration, selective attention, gain control, and circuit plasticity. However, the mechanisms by which this robust circuit motif emerges during early development are largely unknown. We first investigated the temporal profile of synaptic connectivity from VIP INs to SST INs. We found that VIP INs provided functional synaptic connections to SST INs as early as postnatal day (P) 6-7, while pyramidal neurons received synaptic inputs from VIP INs later, starting from P12-13. We then asked how the spontaneous activity of VIP INs during early development affects the connectivity from VIP INs to SST INs and pyramidal cells in adulthood. Alteration of the spontaneous activity of VIP INs during the earlier time window (P5-12), when VIP IN to SST IN connections are established, permanently impaired the synaptic connectivity from VIP INs to SST INs in adulthood. However, the manipulation of VIP INs activity during the later window (P13-20), when VIP INs synapse onto pyramidal cells, did not affect the connectivity from VIP INs to either SST INs or pyramidal cells. The impaired inhibition from VIP INs to SST INs leads to highly synchronized and enhanced activity of SST INs during locomotion. Interestingly, during the period of VIP IN-to-SST IN connectivity establishment, GABA release from VIP INs depolarized SST INs but switched the polarity around P13-14. The suppression of NKCC1 expression in SST INs during this early developmental period led to the decreased inhibition from VIP INs to SST INs in adulthood, implying that the depolarization of SST IN by VIP INs during the synaptic connection period is important for the strong connectivity from VIP INs to SST INs in adulthood. Together, the early synaptic establishment from VIP INs to SST INs, when GABA from VIP INs depolarize SST INs, results in the strong synaptic connection from VIP IN-to-SST IN. Alteration of VIP IN activity or GABA polarity in SST INs during early development leads to permanent impairment in cortical disinhibitory circuits in adulthood.

**Disclosures: S. Lee:** None. **A. Inacio:** None. **P. Stevenson:** None. **J. Qi:** None. **S. Naskar:** None.

**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.13/Web Only

**Topic:** D.05. Auditory & Vestibular Systems

**Title:** Early sensory deprivation influence on infragranular pyramidal neurons in rodent primary auditory cortex

**Authors: *T. MACHARADZE**[1,4], F. OHL[2,4], E. BUDINGER[3,4], J. HENSCHKE[5];
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**Abstract:** Multisensory integration recruits higher-level association cortex, but also first-level sensory areas like the primary auditory (A1), somatosensory (S1), and visual cortex (V1). The underlying anatomical pathways include direct intracortical connections between A1, S1, and V1. We have previously shown that during postnatal development, the anatomical and functional strengths of these intracortical multisensory connections as well as the dendritic morphology and spine density of potential supragranular pyramidal target neurons are substantially altered after early auditory, somatosensory, and visual. Here, we investigated how the loss of early sensory experience influences the dendritic morphology and spine distribution of infragranular pyramidal neurons in A1. Young Mongolian gerbils were deprived by bilateral sciatic nerve transection at postnatal day (P) 5, ototoxic inner hair cell damage at P10 (i.e., before ear canal opening) or eye enucleation at P10 (i.e. before eye opening). At P28, which demarcates the end of the critical period, brain sections of the deprived and control animals were stained using the Golgi-Cox method. Afterwards, the morphology of 36 infragranular pyramidal neurons was studied using the Neuro Lucida system. Sholl- and branch-order analyses showed that early sensory deprivation of either type leads to a slight decrease of the dendritic branching (intersections) and dendritic length in particular of apical dendrites of the layer V pyramidal neurons in A1. The spine number and spine density of basal and apical dendrites are generally increased. This is in some contrast to our previous findings on layer III pyramidal neurons where we observed a general decrease of the spine number and density following somatosensory, auditory and visual deprivation. In conclusion, our results suggest that the loss of early sensory experience induces a refinement of intracortical multisensory connections by a proliferation of dendritic spines in infragranular but a pruning of spines in supragranular layers of A1 in young animals. Based on present and previous own results and on findings from the literature, we propose a developmental scenario for morphological changes of pyramidal neurons in A1 following early sensory deprivation.

**Disclosures:** **T. Macharadze:** None. **F. Ohl:** None. **E. Budinger:** None. **J. Henschke:** None.

**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.14/B12

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

**Support:** NIH Grant DP2 MH125812
Young Investigator Grant from the Brain and Behavior Research Foundation (UMD)
Seed grant from the Brain and Behavior Institute (UMD)

**Title:** Melanopsin-dependent changes in gene expression and synaptic refinement in the developing mouse visual system

**Authors: *R. GUPTA**[1], T. A. ALEXANDER[2], C. ZHANG[3], A. T. BELEW[4], N. M. EL-SAYED[4], C. M. SPEER[3];
[1]CMNS- Biol. Department, Biology-Psychology Building, 144 Room 1225 4094 Campus Drive, [2]Biology, Cell Biol. and Mol. Genetics, Ctr. for Bioinformatics and Computat. Biol., [3]Biol., [4]Cell Biol. and Mol. Genetics, Ctr. for Bioinformatics and Computat. Biol., Univ. of Maryland, College Park, MD

**Abstract:** Light plays an important role in the development of the visual system prior to eye-opening. During the first postnatal week in the mouse, intrinsically photosensitive retinal ganglion cells (ipRGCs) respond to light via the photopigment melanopsin, which drives ipRGC depolarization independently of rod/cone input. Genetic deletion of melanopsin or ablation of ipRGCs has been shown to impact retinal vasculature development, cholinergic spontaneous retinal activity, eye-specific retinogeniculate refinement, and synapse formation in the cortex. However, whether melanopsin signaling regulates molecular changes in ipRGCs or their central targets in the developing brain is not well understood. In this work, we sought to determine whether melanopsin signaling regulates gene expression (in the retina and brain), local protein translation in ipRGCs, and retinofugal synapse formation from M1 type ipRGCs to the brain's master circadian pacemaker, the suprachiasmatic nucleus (SCN). Using a combination of bulk RNA-seq, ipRGC-targeted translating ribosome affinity purification (TRAP), and single-molecule localization super-resolution microscopy we provide evidence for melanopsin-dependent impacts on the development of ipRGCs and their synaptic connections in the SCN prior to eye-opening.

**Disclosures: R. Gupta:** None. **T.A. Alexander:** None. **C. Zhang:** None. **A.T. Belew:** None. **N.M. El-sayed:** None. **C.M. Speer:** None.

**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.15/B13

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

**Support:** NIH R01NS123710
Brain Research Foundation Seed Grant

Paul and Lilah Newton Brain Science Award
Simons Center for Social Brain

**Title:** A Ras-dependent transcriptional regulatory mechanism governs activity-dependent circuit development in the dentate gyrus

**Authors: *J. THOMPSON**, A. XUE, A. BRAWNER, Y. LIN;
Upstate Med. Univ., Syracuse, NY

**Abstract:** During development, changes in neuronal physiology and form are required to meet the demands of adult-level circuit activity. Although recent work has begun to detail how calcium-sensitive gene expression enables developmental changes, regulatory mechanisms that coordinate activity-dependent neuronal maturation remain elusive. We utilized the immediate early gene Npas4 to generate a reporter mouse model (DevATLAS) that tags individual neurons as they begin the process of activity-dependent circuit maturation. We previously established that DevATLAS-tagged dentate gyrus granule cells (GCs) have more active synapses than un-tagged GCs and that DevATLAS GCs functionally contribute to the emerging memory ability in young mice. In this study we utilized multiomic single-nuclei RNAseq and ATACseq to identify transcriptional regulatory mechanisms that contribute to the functional maturity of dentate gyrus circuits. At P20 we reveal the presence of three distinct stages of GC development: immature, growth, and synaptic. These GC subgroups have increasing proportions of DevATLAS-tagged GCs and exhibit distinct transcriptional phenotypes and chromatin landscapes. Our results indicate that a transcription factor known to contribute to dentate gyrus GC development (Klf9) and a Ras-responsive transcription factor (Rreb1) are poised to coordinate activity-dependent GC development. Rreb1 and Klf9 RNA expression significantly varied across GC subgroups and was increased in DevATLAS-tagged GCs. The enrichment of platforms of consecutive, overlapping Rreb1 and Klf9 motifs suggest that these two factors act cooperatively. In addition, Smad3 appears to facilitate the targeting of activity-dependent AP1 transcription factors in synaptically mature, DevATLAS-tagged GCs. Critically, we find that the Rreb1/Klf9/Smad3 transcriptional regulatory program is present in a subset of interneurons within the P20 dentate gyrus sample, indicating that this mechanism may help balance excitation and inhibition in maturing hippocampal circuits. By manipulating this program through elevated Ras activation, we increased the number of active excitatory and inhibitory synapses in vivo, substantiating the relevance of this novel developmental regulatory mechanism.

**Disclosures:** **J. Thompson:** None. **A. Xue:** None. **A. Brawner:** None. **Y. Lin:** None.

**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.16/B14

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

**Support:** Kakenhi 21K06409
Kakenhi 20H03414
Kakenhi 19K22471
Kakenhi 17K07076

**Title:** Two-step collateralization for multiple-targeting of association projections from intra-telencephalic (IT)-type neurons in layer 5a in the mouse cerebral cortex

**Authors:** Y. OKA[1,2], M. YASUMURA[1], K. SEKI[1], M. TANIGUCHI[1], ***M. SATO**[1,2];
[1]Anat. and Neurosci., [2]United Grad. Sch. of Child Develop. (UGSCD), Osaka Univ., Suita-Shi, Japan

**Abstract:** The intra-telencephalic (IT)-type of neurons is one of the major classes of glutamatergic neurons in the cerebral cortex and constitutes association projections that connect the cortical areas. Among the IT-type neurons, those in the primary somatosensory cortex (S1) projecting their axons to the primary motor cortex (M1) are involved in fine regulation of movements both in mice and in humans. Optogenetic inhibition of the activities of IT-type neurons in S1 and M1 in mice disrupts fine regulation of finger movements in handling food pellets for eating. Fiber structure abnormalities between S1 and M1 are correlated with lower behavioral scores for dexterous finger movements in patients of developmental coordination disorders, a frequent comorbid for autism spectrum disorders (ASD). Anatomically, the IT-type neurons are mainly located in layer 2/3 and layer 5a. We previously reported our single neuron analysis demonstrating that in mice, association projections from layer2/3 IT-type neurons in S1 to the motor cortex are formed as the one and the longest interstitial collaterals among those protruding from the earlier extending callosal axons (Oka et al., Cereb. Cortex, 2021). In this study we examined the developmental processes of layer 5a IT-type neurons at a single neuron resolution and compared with those of the layer 2/3 neurons. We found the association projection to the motor cortex by layer 5a neurons in S1 was formed in a similar way with those by layer 2/3 neurons. As expected from the order of their birthdates, layer 5a IT-type neurons projected their cortico-cortical axons earlier than the layer 2/3 IT-type neurons. In some neurons, the longest collateral projecting to the motor cortex had two major sites of ramification, possibly corresponding to future M1 and M2. Interestingly, the branches to the one of the two sites were collaterals from those projecting to the other. Furthermore, few branches of the longest collateral directed to the regions other than the two sites. These results suggest that the target-directed, secondary collateralization may be the underlying mechanisms for multiple-region targeting by a single collateral, which was observed in cortico-cortical projection from the adult mouse V1 and monkey S1.

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**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.17/B15

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

**Support:** NSF GRFP DGE1752814
NIH Grant R00EY028625
NIH Grant R01NS105333
Society of Hellman Fellows
NIH Grant F32NS126310

**Title:** Single-cell transcriptomic analysis of experience-dependent plasticity in mouse whisker somatosensory cortex

**Authors: *S. BUTRUS**, H. R. MONDAY, D. FELDMAN, K. SHEKHAR;
UC Berkeley, Berkeley, CA

**Abstract:** Sensory experience during critical periods sculpts the development of nascent neocortical circuits. Experience-dependent plasticity has been studied extensively in the mouse whisker somatosensory cortex (S1) due to its orderly somatotopic map and ease of manipulating tactile experience by removing whiskers. Previous studies have extensively characterized S1 neurons and circuits, revealing the physiological basis of many features of experience-dependent plasticity. In contrast, the transcriptional changes underlying plasticity during critical periods remain poorly understood, particularly at the resolution of the 100+ transcriptomically distinct cell types that are present in S1. Since 80-90% of autism spectrum disorder patients present tactile hyper- or hypo-sensitivity that may reflect atypical development of S1 circuits, understanding how experience regulates transcriptomic cell type plasticity may shed light on how circuit dysregulation emerges in S1 in autism.
Here, we performed single-nucleus mRNA sequencing (snRNA-seq) on whisker S1 tissue obtained from normal and whisker-deprived mice to determine the experience-dependent molecular changes in this cortical region. To test the hypothesis that whisker experience is required for cell type development in S1, snRNA-seq was performed at two time points spanning two established critical periods in whisker-deprived and control mice. We employed two distinct whisker deprivation paradigms: 1) 1-day deprivation of B- and D-whisker rows from P21 to P22 to induce rapid competitive map plasticity across alternating spared and deprived S1 columns, and 2) a 10-day bilateral full-face deprivation from P12 to P22 to test the overall influence of whisker experience on cell type development. Unsupervised and supervised machine learning approaches (dimensionality reduction, clustering, graph embedding, and classification) were used to identify transcriptomic cell types at each time point and assess the influence of whisker experience on their maturation. After identifying a subset of cell types that were uniquely regulated by development and whisker experience, we conducted hybridization chain reaction fluorescence in situ hybridization (HCR-FISH) experiments targeting candidate genes to validate the cell type-specific experience-dependent alterations observed in the snRNA-seq data. Our findings provide predictions regarding S1 cell types that could be selectively affected by neurodevelopmental disorders such as autism. Our experimental and computational workflows establish a blueprint to test these hypotheses using mouse models of autism spectrum disorder.

**Disclosures: S. Butrus:** None. **H.R. Monday:** None. **D. Feldman:** None. **K. Shekhar:** None.

**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.18/B16

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

**Support:** NWO Grant OCENW.KLEIN.535

**Title:** Acetylcholine shapes spontaneous visual cortex activity in developing mice before eye opening

**Authors: *D. CABRERA-GARCIA**[1], C. LOHMANN[2];
[1]Synapse and Network Develop., Netherlands Inst. for Neurosci., Amsterdam, Netherlands;
[2]Synapse and Network Develop., Netherlands Inst. For Neurosci., Amsterdam, Netherlands

**Abstract:** The neuromodulator acetylcholine is associated with arousal and attention in adult animals, facilitating sensory processing in cortical areas such as the visual cortex. However, how acetylcholine might also mediate behavioral states and spontaneous activity in sensory areas during development remains unclear. Here, we investigated the correlation between acetylcholine dynamics and the neuronal activity in the primary visual cortex (V1) of mice during the second postnatal week, before eye opening. We combined genetically encoded cholinergic and calcium indicators to image the network dynamics with dual-color widefield imaging and the cellular activity with two-photon microscopy. Simultaneously, we evaluated the behavioral states by monitoring the mouse body and facial movements. We found that acetylcholine levels were elevated during active states, showing a positive correlation with both body and facial movements. Furthermore, increased levels of acetylcholine during active behavioral states were associated with changes in spontaneous activity patterns within and between V1 and higher visual areas. At the cellular level, high acetylcholine levels disrupted synchronous activity between neurons, whereas the application of atropine, a muscarinic acetylcholine receptor blocker, enhanced neuronal correlations. Our results highlight the role of acetylcholine in arousal states during development, which may modulate the processing of spontaneous activity in the mouse visual cortex before the onset of visual experience.

**Disclosures: D. Cabrera-Garcia:** None. **C. Lohmann:** None.

**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.19/B17

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

**Support:** NIH Grant DC007695

**Title:** Spontaneous activity drives the synchronous maturation of the calyx of Held nerve terminal and its synaptic target in the medial nucleus of the trapezoid body

**Authors: *D. HELLER**[1], N. BENITES[1], E. AMICK[1], A. DAGOSTIN[2], S. M. YOUNG, Jr[3], H. VON GERSDORFF[2], G. A. SPIROU[1];
[1]Univ. of South Florida, Tampa, FL; [2]Oregon Hlth. & Sci. Univ., Portland, OR; [3]Dept. of Anat. and Cell Biol., Univ. of Iowa, Iowa City, IA

**Abstract:** Synaptogenesis occurs independent of neural activity, but maturation and refinement of nascent connections is an activity-dependent mechanism. Intrinsic patterned spontaneous activity (SA) occurs in several brain regions during development, including the visual and auditory systems. Interestingly, SA in these sensory systems occurs prior to the onset of external stimuli (in mice, ear canals and eyes open after P10), highlighting the importance of SA during neural circuit formation. In the auditory system, intrinsic SA originates embryonically in the cochlea and propagates throughout the ascending auditory pathway. Globular bushy cells (GBCs) located in the ventral cochlear nucleus (VCN) project contralaterally and innervate principal cells (PCs) in the medial nucleus of the trapezoid body (MNTB) forming the calyx of Held (CH) nerve terminal. The CH:MNTB synaptic connection is utilized as a model system for studying the role of SA during neural circuit formation, in part because growth of the CH occurs rapidly (postnatal day (P)2-P6) resulting in mono-innervation, and key biophysical properties have been characterized. Previous manipulations to eliminate SA at the developing CH have involved genetic strategies that also affect cochlear function, and may induce homeostatic compensatory mechanisms in GBCs. To address this confounding factor, we directly manipulated synaptic transmission at the CH:MNTB connection through viral vector mediated, rapid-onset expression of tetanus neurotoxin (TeNT). Following unilateral viral vector injections into the VCN at P0, mCherry fluorescence (co-expressed with TeNT) was detectable within 48 hours in CHs innervating the contralateral MNTB. Whole-cell patch-clamp recordings from transduced P6 PCs (n = 11), compared to control, non-transduced ipsilateral MNTB PCs (n = 12), shows a decrease in the frequency (0.7 ± 0.4 Hz vs 3.2 ± 2.1 Hz; $p < 0.05$), increase in decay rate (1.2 ± 0.3 ms vs 0.7 ± 0.1 ms; $p < 0.05$), and no change in the amplitude (63.0 ± 18.2 pA vs 66.2 ± 15.8 pA; $p = 0.61$) of spontaneous excitatory postsynaptic currents. P6 MNTB PCs innervated by transduced CHs show a delayed transition from tonic to phasic firing (0% phasic/100% tonic vs 93% phasic/17% tonic), where the percentage of phasic PCs at early developmental ages fit to a Boltzmann function resulted in a V50 = P3.5. P9 immunostaining shows impaired growth of the CH expressing TeNT with reduced volume (706 ± 340 $\mu m^3$ vs 1601 ± 294 $\mu m^3$; $p < 0.05$) and increased thickness (2.3 ± 0.6 μm vs 1.3 ± 0.2 μm; $p < 0.05$). This study is ongoing and highlights an important role for SA triggering rapid growth of the CH and the synchronous maturation of the MNTB PC biophysical properties.

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**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.20/B18

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

**Support:** MIT-Italy Universita' di Pisa Seed Fund
EU H2020 MSCA ITN project "Serotonin and Beyond" (N 953327)

**Title:** Fluoxetine treatment early in life induces permanent alterations to the serotonin circuitry

**Authors:** S. NAZZI[1], G. MADDALONI[1,2], S. MIGLIARINI[1], M. PICCHI[1], N. BARSOTTI[1], ***M. PASQUALETTI**[1,3];
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**Abstract:** Serotonergic neurons of the brainstem provide a profuse innervation to the whole central nervous system. As previously shown, interfering genetically or pharmacologically (fluoxetine treatment) with serotonin (5-HT) homeostasis in the adult is sufficient to alter reversibly the correct serotonergic axonal wiring, suggesting that proper serotonin homeostasis in the adult brain is crucial to preserve circuitry and that 5-HT fibers maintain a high degree of structural plasticity to adulthood, being bidirectionally reshaped by fluctuations of 5-HT content[1-3]. Here we investigate whether fluoxetine treatment early in life impacts 5-HT circuitry, and whether this is reversible or lifelong. To this aim, we chronically treated Tph2-GFP knock-in heterozygous mice with the antidepressant fluoxetine early in life, and combined GFP immunofluorescence with confocal microscope imaging for 3D-reconstruction of serotonergic fibers from birth to adulthood. Results revealed that mice exposed to fluoxetine, in addition to the expected appearance of anxiety- and depression-like behaviors[4] (i.e. paradoxical behavior), they also showed a dramatic reduction density of 5-HT fibers innervating the hippocampus. These data suggest that fluoxetine induced permanent remodeling of the serotonergic circuitry and that this may contribute, at least in part, in mediating the induced paradoxical behavior.
[1] Migliarini et al 2013. PMID: 23007167 [2] Pratelli et al, 2017. PMID: 28413824 [3] Nazzi et al, 2019. PMID: 31243951 [4] Ansorge et al, PMID: 15514160

**Disclosures: S. Nazzi:** None. **G. Maddaloni:** None. **S. Migliarini:** None. **M. Picchi:** None. **N. Barsotti:** None. **M. Pasqualetti:** None.

**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.21/B19

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

**Support:** NIH R01
NIH R21

**Title:** Evaluating The Role Of Serotonin Receptors In Modulating Neuronal Circuits During Experience Dependent Critical Period Plasticity

**Authors: *A. MALLICK**[1], J. EPSTEIN[1], H. TAN[1], A. M. DACKS[2], Q. GAUDRY[1];
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**Abstract:** The onset of sensory experiences in the early life critical period of an organism regulates neuronal circuit reprogramming and refinement. During this brief time window, external and internal factors modify brain networks that in turn enable the proper development of sensory circuits. Studies on critical period plasticity (CPP) in mammals have shown that along with sensory experiences, neuromodulators also play an important role in guiding the direction of plasticity during the critical period. However, the mechanisms by which CPP is affected by neuromodulators like serotonin (5-HT) is unclear. Here, we employ the genetically amenable primary olfactory processing center of the *Drosophila melanogaster* to study the role of serotonin in CPP. We used previously established odor exposure protocols to induce structural plasticity in the $CO_2$ specific V-glomerulus to investigate the role of 5-HT in modulating the olfactory circuit during the critical period. We find that blocking the release of synaptic 5-HT in the antennal lobe prevents structural plasticity in the V-glomerulus following chronic 5% $CO_2$ exposure. We also identified serotonin receptors (5-HTRs) 5HT1B, 5-HT2B and 5-HT7 as required for CPP. Knocking down 5-HT2B in the $CO_2$ specific olfactory sensory neurons (OSNs) was not sufficient to block CPP but knocking down this receptor in all OSNs was sufficient to block CPP. Also, knocking down NMDA receptor-2 (NMDAR-2) or *NR2* receptors in the $CO_2$ specific OSNs was sufficient to impede critical period plasticity. We hypothesize that serotonin signaling in the OSNs might act through 5-HT2B to modulate NMDAR activity in the cognate glomerulus and influence structural plasticity as seen in *in vitro* studies in mammals. Furthermore, 5-HT7 receptor expression by a subset of GABAergic local interneurons (LNs) was also required for CPP. Our results are congruous with recent studies that showed the involvement of GABAergic inhibition in the *Drosophila* antennal lobe during the critical period. Taken together, our results indicate that serotonin modulates both the cognate sensory circuit through OSNs and the global inhibitory circuit through LNs to promote structural plasticity in the V glomerulus during the critical period.

**Disclosures: A. Mallick:** None. **J. Epstein:** None. **H. Tan:** None. **A.M. Dacks:** None. **Q. Gaudry:** None.

**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.22/B20

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

**Support:** ZIAMH002898

**Title:** Widespread transduction of the primate brain with prenatal delivery of adeno-associated viral vectors

**Authors: *A. RIBEIRO GOMES**[1], N. HAMEL[1], S. MASTWAL[1], D. C. IDE[2], G. DOLD[2], C. T. RICHIE[4], T. USDIN[3], K. H. WANG[5], D. A. LEOPOLD[1];
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**Abstract:** Viral gene delivery systems extend our ability to dissect genetic and molecular mechanisms that guide the development and function of nervous systems. In non-human primates (NHPs), the establishment of transgenic animals is time-consuming, labor-intensive, and costly, restricting the genetic tractability of neural circuitry in primates. Recent work with recombinant adeno-associated viruses (AAV) has shown examples of early, widespread introduction of transgenes across the brain, providing safe and long-term access to defined cell populations. In the present study we aimed to apply this work to NHPs by developing a minimally invasive nonsurgical technique for efficient AAV-mediated transduction of the fetal brain. Ultrasound visualization was used to deliver AAV vectors into the cerebroventricular system, allowing cell transduction at different developmental stages. After first establishing this method in rats, we now use this technique to routinely deliver AAV vectors to the nervous system of both rats and marmosets. This approach results in dense and ubiquitous transgene expression throughout the brain, particularly in the cerebral cortex, and additional structures within the central and peripheral nervous system. Restriction of gene expression can then be achieved through the postconception timing of the injections as well as use of cell-type specific promoters and enhancers. For instance, we recently implemented an intersectional strategy in marmosets, using AAV-based nestin-dependent expression of Cre recombinase, to selectively transduce cells born or in very early stages of differentiation within a certain time window. Co-delivery of the nestin-Cre construct with Cre-dependent AAV vectors in the third trimester of pregnancy isolated late-born neurons in selected regions of the brain, such as the rostral and medial migratory streams. The widespread and rapid onset of transgene expression starting in the womb offers new experimental opportunities to study the establishment, maturation, and plasticity of anatomical and functional circuits most critical to human cognition.

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**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.23/Web Only

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

**Support:** NIH Grant R01-NS119472

**Title:** Functional characterization of long-term forebrain organoid cultures using longitudinal multiphoton calcium imaging

**Authors: *B. REES**[1,2], P. HARARY[1], K. G. MENSAH-BROWN[1], D. JGAMADZE[1], H. SONG[2], G.-L. MING[2], H. CHEN[1];
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**Abstract:** Understanding the developmental trajectory of functional activity of human brain organoids is highly relevant to their use as a tool to study neurological conditions as well as a substrate for transplantation-based neural repair. The ability of calcium imaging analysis to capture the activity and spatial location of a large number of neurons is highly valuable, especially given the rudimentary laminar architecture present in cortical organoids. In addition, this non-terminal approach enables longitudinal analysis of the same organoid samples. Here, the genetically encoded calcium indicator GCaMP8m and a custom-designed culture plate were used to perform longitudinal multiphoton imaging of forebrain organoids, offering increased spatial resolution of organoid neural activity without perturbing organoid growth in suspension. Organoids were grown from an induced pluripotent stem cell line derived from a healthy volunteer. At differentiation day (dd) 40, the organoids were sliced at a thickness of 500μm, with repeated slicing every 30 days. Viral transduction was performed on dd45 with AAV expressing GCaMP8m under a human synapsin promoter. Neural activity was assessed at two time points: dd120 and dd180 (n=7 organoids). Analysis of the videos was performed in MATLAB. Motion correction was performed using the FluoroSNNAP platform, region of interest (ROI) selection was performed using an adapted version of the EZCalcium toolbox, and custom scripts were created for further analysis. Calcium transient events were identified and the timing of the events was used to explore functional characteristics of the organoids and their evolution as they matured. As compared to dd120 organoids, timing measures such as a reduction in inter-transient interval and an increase in events per minute indicated elevated frequency of activity in the dd180 organoids. Further, measures of synchronicity and connectivity, such as the spike time tiling coefficient and Pearson's correlation coefficient respectively, indicated the potential emergence of synchronous, non-homogenous neural populations in the maturing organoid. These results suggest that long-term brain organoids cultures undergo functional maturation, yielding more complex neural behavior as they develop. Taken together, these findings help create a foundation for understanding the developmental trajectory of neural activity in long-term organoid cultures.

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**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.24/B21

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

**Support:** JST SPRING, JPMJSP2104 to AN
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JSPS, KAKENHI 21K18245 to TI
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**Title:** Elucidating developmental stage-specific roles of NMDA receptors in neural circuit refinement using a rapid protein knockdown system

**Authors: *A. NIHASHI**[1,4], N. NAKAGAWA[1,4], T. SATO[1], R. AJIMA[6,5,2], Y. SAGA[2], M. KANEMAKI[3,4], T. IWASATO[1,4];
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**Abstract:** Precise neuronal connectivity underlying higher brain functions in mammals is established through activity-dependent circuit reorganization during postnatal development. We and others previously found that the NMDA-type glutamate receptors (NMDA receptors) play a crucial role in circuit refinement using gene knockout techniques (e.g. Iwasato et al., Neuron 1997, Nature 2000; Mizuno et al., Neuron 2014). In the barrel cortex, layer 4 (L4) spiny stellate neurons expand their basal dendrites asymmetrically toward the barrel center, where termini of thalamocortical axons transmitting information from a single whisker form a cluster. Since these morphological features of barrel cortex L4 neuron dendrites are formed during neonatal stages in an activity-dependent manner, dendrite refinement of these neurons is an excellent model for developmental circuit refinement. Single-cell knockout of NR1, the essential NMDA receptor subunit, impairs dendrite asymmetry of L4 neurons in the mouse barrel cortex, suggesting cell-autonomous functions of NMDA receptors in dendritic refinement (Mizuno et al., 2014). However, because there is no gene knockout system whose temporal control is sufficiently fast, roles of NMDA receptors in specific steps of dendritic refinement remain unexplored. To address this issue, we here used the auxin-inducible degron 2 (AID2) technology, which is a recently developed protein knockdown system (Yesbolatova et al., Nature Commun. 2020). With this system, 5-Ph-IAA administration induces depletion of a target protein fused with an mAID tag in the presence of the OsTIR1(F74G). By using EGFP-mAID reporter mice, we found that the AID2 enables to knock down the reporter protein efficiently and rapidly in the postnatal mouse brain. We then generated NR1-mAID knock-in mice and found that these mice die soon after birth if 5-Ph-IAA is administered via mother. This phenotype is similar to NR1 global knockout

mice, suggesting that the synaptic NR1-mAID protein is an effective target of the AID2. Developmental stage-specific roles of NMDA receptors in dendrite refinement of barrel cortex L4 neurons revealed by using the AID2 will be discussed.

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**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.25/B22

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

**Support:** ANR-SynDev-R22093AA
ERC-Synergy Hope

**Title:** Characterization of hippocampal neuronal activity during the first postnatal week in vivo

**Authors: *S. MORTET**, P.-P. LENCK-SANTINI, A. BAUDE, R. COSSART;
INMED, Marseille, France

**Abstract:** The proper establishment of neuronal networks during development is critical to the correct functioning of the nervous system in adulthood. In the rodent hippocampus, during the first post-natal week, immature neuronal networks are characterized by spontaneous network activites (SNA) that synchronize large populations of neurons. It is believed that SNAs play a critical role in the neuronal network organization and function. In vitro, SNA are generated by internal hippocampal networks and particulary GABAergic interneurons. While GABAergic neuronal activity plays a critical role in SNA generation in vitro, recent evidence suggests that this may not be the case in-vivo. Indeed, in vivo, SNA called ‘early sharp waves’ (eSPWs), are triggered by spontaneous myoclonic contractions transmitted via the entorhinal cortex (Valeeva and al., 2019). How immature hippocampal neurons integrate eSPW information is still poorly understood. Here, combining extra-cellular electrophysiology with optogenetics in transgenic neonatal mice, we investigated how in-vivo neonatal SNA modulates the activity of on different classes of hippocampal neurons. We observed that the response of CA1 hippocampal neurons during eSPWs is heterogeneous: while 60% of neurons fire strongly at the onset of eSPWs, 5% fire moderately at the offset and 35% do not change their activity. The proportion of onset neurons decreases with age, leaving place to a majority (75%) of offset neurons in the end of the first post-natal week. However, it seems to be no difference between glutamatergic and GABAergic neurons (located above the pyramidal layer) activity during eSPWs. But we observed a majority (80% at postnatal day -P-4) of neurons that are located bellow the pyramidal cell layer are of the onset type, suggesting that they are strongly recruited during eSPWs. Given their anatomical location, these neurons are likely of the GABAergic type. We are currently investigating their putative GABAergic identity. The fact that a subclass of hippocampal neurons

is strongly activated at the onset of eSPWs suggests that these neurons may play an important role in the establishment of hippocampal networks.

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**Poster**

**PSTR002. Neural Circuit Maturation and Remodeling: From Synapses to Sensory Systems**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR002.26/B23

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

**Support:** JST ERATO JPMJER1801
JSPS Grants-in-Aid for Scientific Research 18H05525
JSPS Grants-in-Aid for Scientific Research 20K15926

**Title:** Artificially induced synaptic pairs exhibit similar orientation selectivity

**Authors: *T. KASHIMA**[1], T. YOSHIDA[2,3,4], K. OHKI[2,3,4], Y. IKEGAYA[1,3];
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**Abstract:** The proper development of neural circuits is paramount for normal brain function. A long-standing hypothesis for the rule of neural connections is the Hebbian rule, which proposes that neurons that fire together wire together. However, there has been no direct evidence of this role, and its impact on brain function has remained elusive. In this study, we sought evidence for the Hebbian rule by artificially inducing synchronous firing during the developmental process of neural circuit formation in the mouse visual cortex, a region known for its structural-physiological correlation between neural circuit designs and brain function. Using non-invasive transcranial optogenetic stimulation, we induced synchronous firing in ChR2-positive neurons during the critical developmental period. Subsequent investigations revealed a higher probability of connections between synchronously fired neurons compared to ChR2-negative neurons or control w/o-optostimulation groups. Two-photon calcium imaging of the orientation selectivity of stimulated neurons revealed that synchronously fired neurons exhibited similar orientation selectivity. Considering previous studies that neurons with similar orientation selectivity have a higher probability of connection, these results suggest that developmental synchronous firing influences the formation of synaptic connections and may play a role in shaping brain function.

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**Poster**

**PSTR003. ADHD, SLI, Dyslexia, and other Specific Disorders of Neurobehavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR003.01/B24

**Topic:** A.07. Developmental Disorders

**Support:** MOST110-2320-B-004-001
MOST111-2320-B-004-002
IFCR 2015-2020

**Title:** Developmental tuning of neuronal excitability and concomitant regulation of transcriptome by cyclin-dependent kinase-like 5

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**Abstract:** Cyclin-dependent kinase-like 5 (CDKL5) is a serine-threonine kinase enriched in the forebrain to regulate neuronal development and function. Patients with CDKL5 deficiency disorder (CDD), a severe neurodevelopmental disorder caused by mutations of *CDKL5* gene, present early-onset epilepsy as the most prominent feature. However, spontaneous seizures have not been reported in neonates of CDD mouse models, raising vital questions on the human-mouse discrepancy and the roles of CDKL5 in early postnatal brains. Here, we firstly measured electroencephalographic (EEG) activities via a wireless telemetry system coupled with video-recording in neonatal mice. We found that mice lacking CDKL5 exhibited spontaneous epileptic EEG discharges, accompanied with increased burst activities and ictal behaviors, specifically at postnatal day 12 (P12). Intriguingly, those epileptic spikes disappeared after P14. We next performed an unbiased transcriptome profiling in the dorsal hippocampus and motor cortex of *Cdkl5* null mice at different developmental timepoints, uncovering a set of age-dependent and brain region-specific alterations of gene expression in parallel with the transient display of epileptic activities. Finally, the gene expression alterations of multiple differentially expressed genes (DEGs) were validated at the transcript as well as the protein levels, supporting the relevance of these genes to CDKL5-regulated neuronal excitability. Our findings revealed early-onset neuronal hyperexcitability in mouse model of CDD and identified novel molecular targets to tackle neonatal epilepsy, providing new insights into the etiology of CDD.

**Disclosures: W. Liao:** None. **K. Lee:** None.

**Poster**

**PSTR003. ADHD, SLI, Dyslexia, and other Specific Disorders of Neurobehavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR003.02/B25

**Topic:** A.07. Developmental Disorders

**Support:** R01NS107428

**Title:** Neuron navigator 3: An early neurogenesis protein with variants causing intellectual disability, global developmental delay and microcephaly

**Authors: *A. GHAFFAR**[1,2], P. STRØMME[3], A. KHAN[5], B. ISIDOR[6], C. CHIAVERINI[7], A. INNES[8], M. SCHWARTZ[9], M. ZECH[10], E. FRENGEN[4], D. MISCEO[4], J. HELLE[3], M. UMAIR[11], B. COGNÉ[6], A.-L. BRUEL[12], A. SORLIN[12], P. KUENTZ[12], C. SOMERVILLE[9], Z. AHMED[2], S. RIAZUDDIN[13], S. RIAZUDDIN[2];
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**Abstract:** Microtubule associated proteins (MAPs) are mostly expressed throughout the central nervous system and are involved in cell proliferation, myelination, neurite formation, axon specification, outgrowth, dendrite, and synapse formation. Here, we report 12 individuals from eight families harboring predicted pathogenic variants in *NAV3* gene, encoding neuron navigator 3 (NAV3) a microtubule positive tip protein known to be involved in organogenesis. All the affected individuals have intellectual disability (ID). However, some affected individuals also demonstrate other clinical features, including microcephaly, skeletal deformities, eye anomalies and behavioral problems. *In silico* analysis of human fetal RNA expression from public databases revealed *NAV3* expressed throughout the nervous system, with more prominent expression in postmitotic, excitatory, inhibiting, and sensory neurons. When over-expressed, wild type and most of the ID-associated variants, except p.Trp332*, harboring NAV3 in COS7 cells form dendrite like growths, typically required for axonal outgrowth. However, we also observed ID-variants harboring NAV3 proteins cause instability of microtubules in the presence of the microtubule inhibiting drug nocodazole. Finally, our *nav3* zebrafish morphants based study show developmental abnormalities, behavioral deficits, and microcephaly. Specifically, midbrain and hindbrain regions show reduced outgrowth of neurons. Collectively, our data show involvement of *NAV3* in early neurogenesis along with visionary and neuromuscular responses and identify it as a new ID-causing candidate gene in humans.

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**Poster**

**PSTR003. ADHD, SLI, Dyslexia, and other Specific Disorders of Neurobehavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR003.03/B26

**Topic:** A.07. Developmental Disorders

**Support:** NSERC (RGPIN-217-05510)
FRQS (283473)
FMSS

**Title:** Investigating the relationship between intracortical processes, executive functions, and brain structure in healthy children.

**Authors: *S. REMAHI**[1], M. LANGLOIS[2], S. COTE[3], F. RHEAULT[4], M. DESCOTEAUX[4], K. WHITTINGSTALL[3], J.-F. LEPAGE[2];
[2]Pediatrics, [3]Nuclear Medecine, [4]Computer Sci., [1]Univ. de Sherbrooke, Sherbrooke, QC, Canada

**Abstract:** Children with ADHD show poorer executive functions and motor skills compared to typically developing children. Interestingly, paired-pulse transcranial magnetic stimulation (TMS) measures of intracortical function, notably short intracortical inhibition (SICI), has been shown to be lower in children with ADHD, and related to symptom severity. However, it is yet unclear if this relationship extends to ADHD-related symptoms, including alterations in motor skills and executive function, in non-ADHD, typically developing children. Additionally, the physical determinants of TMS response in healthy children remain unknown. Thus, the goals of this study were to: 1) investigate the relationship between intracortical processes, executive functions, and motor dexterity in healthy children; and 2) assess the link between TMS measures and physical elements related to neuroanatomy (scalp-to-cortex distance (SCD), cortical thickness (CT), and apparent fiber density (AFD)). 21 healthy children aged 9-10 were recruited and underwent an extensive TMS protocol, including the main measures of intracortical function, and an MRI session consisting of an anatomical T1, and a diffusion sequences (64 directions). The Behaviour Rating Inventory of Executive Function (BRIEF) questionnaire was completed by parents and the Grooved Pegboard test was administered to assess dexterity. For the first aim, Spearman correlations and general linear models were performed, with BRIEF and Grooved Pegboard scores as outcome variables, and TMS measurements as predictors. Preliminary results show a significant correlation between intracortical facilitation (ICF; ISI 10ms) and the total number of pegs inserted with the dominant hand on the Grooved Pegboard ($r = -0.58$; $p = 0.02$), as well as between the baseline motor evoked potential (MEP) amplitude and the initiative subscale of the BRIEF ($r = 0.53$; $p = 0.03$). However, no significant regression models were observed between TMS measurements, executive function, and motor skills. For the second aim, the same statistical approach was used using this time TMS measurements as outcome variables and brain measurements as predictors. ICF 10 and 15ms significantly correlated with SCD ($rICF10 = -0.58$; $rICF15 = -0.69$; $pICF10 = 0.01$; $pICF15 = 0.0006$). Models for both ICF 10 and 15ms also came out as significant ($pICF10 = 0.08$; $pICF15 = 0.03$) with SCD being the main predictor ($pICF10 = 0.03$; $pICF15 = 0.007$). These results raise questions about the developmental gap in motor and executive functions between typically developing children and

those with ADHD. They also show how SCD can influence the measurement of TMS derived metrics in children.

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**Poster**

**PSTR003. ADHD, SLI, Dyslexia, and other Specific Disorders of Neurobehavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR003.04/B27

**Topic:** A.07. Developmental Disorders

**Support:** SuRE grant: 226141380A
NIH SURE: Genetic dissection of dementia

**Title:** Kekkon5 interacts with dopamine for inhibitory control

**Authors: *J. AGUIRRE**, B. HERNANDEZ, P. SABANDAL, E. B. SALDES, K.-A. HAN; Col. of Sci., the Univ. of Texas at El Paso, El Paso, TX

**Abstract:** Abnormal dopamine signaling is involved in neurodevelopmental disorders such as ADHD, autism spectrum disorder and substance use disorder. The underlying mechanism, however, remains largely unclear. To address this knowledge gap, we performed an unbiased genetic screen for the genes interacting with dopamine signaling for dysfunctional inhibitory control in *Drosophila*. One of the genes we found is *Kekkon5* (*kek5*), the homolog of human LRFN1 (Leucine Rich Fibronectin 1). While the heterozygous *kek5* or *fumin* (dopamine transporter mutant) flies display normal inhibitory control, the double heterozygous *kek5*/+; *fmn*/+ flies show dysfunctional inhibitory control. *Kek5* codes for a synaptic adhesion molecule and is a negative regulator of the Bone Morphogenetic Protein signaling pathway. Kek5 is mainly expressed in the mushroom body αβ neurons. Thus, we hypothesize that Kek5 in the mushroom body αβ lobes interact with the presynaptic dopamine neurons for inhibitory control. We are currently testing this hypothesis. This study will advance the knowledge about the mechanism by which cell adhesion molecules play a role in inhibitory control.

**Disclosures: J. Aguirre:** None. **B. Hernandez:** None. **P. Sabandal:** None. **E.B. Saldes:** None. **K. Han:** None.

**Poster**

**PSTR003. ADHD, SLI, Dyslexia, and other Specific Disorders of Neurobehavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR003.05/B28

**Topic:** A.07. Developmental Disorders

**Title:** Parahippocampal Cortical Thickness Mediates the Effect of Preterm Birth on Cognitive Function

**Authors: *K. DIMITROPOULOU**[1], P. LIN[2], S. LEE[2];
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**Abstract:** Cortical thickness is an index of neurodevelopment and presents a U-shaped trajectory from childhood to late adolescence. Studies suggest reduced cortical thickness in children born <37 weeks, but the associations between cortical thickness in late childhood (8-10 years) and cognitive abilities are not well understood. We examined differences in cortical thickness and their association to cognitive abilities in children with/without a history of premature birth, without medical problems. We used baseline data from the ABCD study. Data Release 4.0 (October 2021), which included 11875 children (M=9.9 y, SD=0.62) from 21 sites nationwide (USA). Children without a medical diagnosis with gestation <37 weeks(premature) and full-term peers were included. We excluded children with missing data for prematurity, and/or cognitive ability and twins. The sample size was 10,235 (87.7% born full-term & 12.3% preterm). Cortical thickness measurements included 35 regions/hemisphere (Desikan-Killiany atlas). We conducted linear mixed-effects models for the association between cortical thickness and preterm birth status controlling for: Age, Sex, Race, Ethnicity, Puberty, Marital Status, Parental Education, Parental Substance Use and scanner/sites (21 sites). We used the NIH toolbox, for total cognitive ability, fluid cognition (real-time processes) and crystalized cognition (e.g. memory). Children born<37w., exhibit distinct patterns of regional cortical thickness that significantly differ (27 brain regions) from those of the full-term peers. Children born<37 w presented increased cortical thickness in the left entorhinal cortex, left parahippocampal gyrus, left rostral anterior cingulate cortex, cuneus (left/right), lateral occipital (left/right), lateral orbitofrontal (left/right), medial orbitofrontal (left/right), peri calcarine (left/right), and right superior frontal gyrus. In contrast, children born<37 w presented more cortical thinning in the left inferior parietal lobule, caudal middle frontal gyrus (left/right), middle temporal gyrus (left/right), pars orbitalis (left/right), pars triangularis (left/right), rostral middle frontal gyrus(left/right), right transverse temporal gyrus, and right insula. Causal mediation analysis on the 27 brain regions demonstrated that the effect of preterm birth on cognitive abilities (Total Cognition & Crystallized Composite) is partially mediated by increased thickness in the left hippocampus (p=0.0008). Findings suggest that there is a difference in cortical thickness in regions related to memory and these differences may be related to cognitive abilities that rely on memory.

**Disclosures: K. Dimitropoulou:** None. **P. Lin:** None. **S. Lee:** None.

**Poster**

**PSTR003. ADHD, SLI, Dyslexia, and other Specific Disorders of Neurobehavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR003.06/B29

**Topic:** A.07. Developmental Disorders

**Title:** Impact of cerebellar neuromodulation on reading speed and accuracy in developmental dyslexia

**Authors: *M. M. LEE**[1,2], L. C. RICE[3,4,2], H. YOUNESIE[2], C. J. STOODLEY[2];
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**Abstract:** Developmental dyslexia (DD) is a prevalent developmental condition characterized by difficulties in reading despite typical educational opportunity and cognitive ability. While the cause of dyslexia is debated, heavy emphasis has been placed on difficulties with phonological decoding, though not all DD diagnoses manifest in this way. DD can also be characterized by slow, laborious reading, reflected in timed reading fluency tasks. The neural underpinnings of untimed reading have been extensively investigated, but less is known about the neural correlates of reading fluency and how reading becomes fast and automatic. The cerebellum may contribute to automatizing cognitive abilities and is well-positioned to support rapid, fluent reading. Right-lateralized posterolateral cerebellar regions are engaged during a range of reading and reading-related tasks and are functionally connected to the cortical reading network, and cerebellar activation patterns have been associated with poor fluency metrics in DD children. To determine whether the right posterolateral cerebellum is a specific modulator of reading fluency, we examined the effect of transcranial direct current stimulation (tDCS) targeting the right posterolateral cerebellum (lobules VI/VII) on reading speed, reading accuracy, rapid naming, and general processing speed in a sample of young adults with typical reading development (n = 25, 19.9 ± 2.0 yrs) and with a diagnosis of DD (n = 9 to date; 19.4 ± 2.3 yrs). Participants completed a battery of reading (accuracy, fluency), rapid naming, and processing speed measures after 20 minutes of 2mA anodal (excitatory), cathodal (inhibitory), or sham (control) tDCS in a within-subjects design. We predicted that right cerebellar tDCS would specifically impact reading fluency and rapid naming measures without affecting reading accuracy or general processing speed. In the readers with typical reading development, cathodal tDCS disrupted reading fluency ($p_{uncorrected} = 0.02$) without impacting reading accuracy, rapid naming, or general processing speed measures. In the DD group, preliminary results suggest cathodal cerebellar tDCS disrupted reading accuracy ($p_{uncorrected} = 0.052$) relative to sham tDCS, with no impact on other measures. Future analyses will also compare DD results directly to individuals with typical reading ability to determine if the cerebellum differentially contributes to reading in these populations.

**Disclosures:** **M.M. Lee:** None. **L.C. Rice:** None. **H. Younesie:** None. **C.J. Stoodley:** None.

**Poster**

**PSTR003. ADHD, SLI, Dyslexia, and other Specific Disorders of Neurobehavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR003.07/B30

**Topic:** A.07. Developmental Disorders

**Title:** Time-based interventions at early ages to reduce ADHD related behavior: preference for immediate-small rewards

**Authors: *G. OCHOA-ZENDEJAS**[1], C. VALERIO DOS SANTOS[2], J. BURITICÁ[2];
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**Abstract:** Perception of time seems to be associated with symptoms of ADHD. Research suggests that individuals diagnosed with ADHDmay experience a subjectively accelerated sense of time and reduced accuracy in estimation of the duration of events. Choosing a small immediate reward over a larger delayed reward is considered Impulsive choice, especially when the larger reward is objectively optimal in terms of potential long-term gains. The purpose of this study was to determine the effects of two behavioral interventions targeting temporal estimation on early-age rats, to reduce impulsive choice in adulthood. Twenty-four male and twenty-four female Wistar rats were divided into four groups. At early ages, the rats had free access to food but were deprived of water for 14 hours per day. Half of the subjects (n = 24) were exposed to a Differential Reinforcement of Low Rates (DRL10 s) schedule, and the rest to a Variable Interval (VI 10 s) schedule between postnatal days 25-40, with milk-formula as reinforcement. At postnatal day 90, the rats were exposed to a delay discounting task while being food-deprived and maintained at 85 % of their *ad libitum* weight. Forty-five-milligram pellets were delivered as reinforcement. A reduction in preference for the impulsive alternative was observed in the majority of the subjects. Additionally, differences between sexes and interventions were found. Preliminary results indicate that early behavioral interventions targeting temporal estimation may have an effect on impulsive choice in adulthood. These findings could contribute to developing interventions for individuals with ADHD diagnosis, as they tend to showcase more impulsive choices in intertemporal choice tasks due likely to difficulties in delaying gratification and making decisions that involve waiting for long-term rewards.

**Disclosures: G. Ochoa-Zendejas:** None. **C. Valerio dos Santos:** None. **J. Buriticá:** None.

**Poster**

**PSTR003. ADHD, SLI, Dyslexia, and other Specific Disorders of Neurobehavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR003.08/B31

**Topic:** A.07. Developmental Disorders

**Support:** FAPESP 2019/15151-0
FAPESP 2023/02947-7
CNPq 314158/2020-0

**Title:** Sensory-motor training improvement in reading performance and eye movement in children with dyslexia

**Authors: *J. A. BARELA**[1], C. SILVA[2], P. R. JESUS[2], M. T. B. DUMAS[2], A. M. F. BARELA[3], G. A. FIGUEIREDO[2];
[1]Inst. of Biosci., [2]Univ. Estadual Paulista, Rio Claro, Brazil; [3]Univ. Cruzeiro Do Sul, Sao Paulo, Brazil

**Abstract:** Dyslexia is associated to deficient literacy, reading and writing, despite adequate intellectual ability and sufficient education provision. However, several studies have shown that besides phonological deficits, children with dyslexia also show poor motor coordination and postural control that might be related to the use of sensory cues to their actions accurately. A few studies have shown improvement in reading performance due to active video games and specific oculomotor training. Therefore, the goal of this study was to examine the effects of a sensory-motor intervention in reading performance and eye movements of children with dyslexia. Ten dyslexic children (11.1± 2.2 years old) performed texts reading displayed in an IPad (12.9") while wearing an eye-tracking system (ETG-SMI 2.0). Total reading time was computed by inspecting the eye coordinates and fixation and saccades were also obtained during reading. Afterwards, children were enrolled in a 2-month intervention motor activity program, composed of 50-min sessions with lomocotor, balance, and manipulative activities, twice a week. In the remaining days, children performed computer based oculomotor activities (visual rapid memory, motion detection, saccades to the right, and saccades to the next line), three times a week, lasting about 15-min. After the 2-month intervention, children performed the reading test again. Results showed that total reading time decreased after the intervention varying from 10 to 20%. Results also showed that fixation and saccades frequency decreased and fixation duration during reading increased after the intervention program. These results suggest that the combination of motor and eye movement training can improve reading performance in dyslexic children and that such improvement is related to eye movement changes during reading.

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**Poster**

**PSTR003. ADHD, SLI, Dyslexia, and other Specific Disorders of Neurobehavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR003.09/B32

**Topic:** A.07. Developmental Disorders

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NIH Grant R01NS092876
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Gates Foundation Grant OPP1119489

**Title:** Effects of fetal EtOH exposure in humans on biomarkers of affective dysregulation

**Authors: *M. E. SELZER**[1], N. DARBINIAN[2], N. MERABOVA[3], G. TATEVOSIAN[3], M. F. MORRISON[4], A. DARBINYAN[6], H. ZHAO[5], L. GOETZL[7];
[1]Neurology; Neural Sci., Lewis Katz Sch. of Med. At Temple Univ., Philadelphia, PA; [2]Shriners Hosp. Pediatric Res. Ctr., Temple Univ., Philadelphia, PA; [3]Med. Col. of Wisconsin-Prevea Hlth., Green Bay, WI; [4]Psychiatry; Ctr. for Substance Abuse Res., [5]Ctr. for Biostatistics and Epidemiology, Dept. of Biomed. Educ. and Data Sci., Lewis Katz Sch. of Medicine, Temple Univ., Philadelphia, PA; [6]Pathology, Yale Univ. Sch. of Med., New Haven, CT; [7]Obstetrics and Gynecology, Univ. of Texas, Houston, Houston, TX

**Abstract: Introduction**: Children with fetal alcohol spectrum disorders (FASD) exhibit behavioral and affective dysregulation, including hyperactivity and depression. Activities in serotonergic (5-HT) and dopaminergic (DA) signal transmission regulate mood, so abnormal monoaminergic signaling might be present, even prenatally. Many women who use alcohol (EtOH) during pregnancy suffer from comorbid depression, and take selective serotonin reuptake inhibitors (SSRIs), which might influence these monoaminergic pathways in the fetus. Alternatively, monoaminergic pathway abnormalities might be a direct effect of EtOH on the fetal brain. To distinguish between these possibilities and determine whether monoaminergic pathway constituents might serve as markers for the affective dysregulation seen in FASD, we measured their expressions in fetal brains and in fetal-derived brain exosomes (FB-Es) isolated from the mothers' blood. **Methods**: Fetal brain tissues and maternal blood were collected at 9-23 weeks of pregnancy. EtOH groups were compared with unexposed controls matched for gestational age (GA). The expression of 84 genes associated with DA and 5-HT pathways were analyzed by qRT-PCR on microarrays. FB-Es also were assayed for serotonin transporter protein (SERT) and brain-derived neurotrophic factor (BDNF) by ELISA. **Results:** Six EtOH-exposed human fetal brain samples were compared to SSRI- or polydrug-exposed samples and to unexposed controls. EtOH exposure was associated with dysregulation of serotonin and DA signaling. DA receptors D3 and D4, and 5-HT receptor HTR2C were upregulated 4-fold, while HTR3A and HTR4 were downregulated. Monoamine oxidase A (MAOA), MAOB and caspase-3 were upregulated 4-30-fold, while mitogen-activated protein kinase 1 (MAPK1) and the serine/threonine kinase AKT were downregulated 9-20-fold. ETOH was associated with 9-fold upregulation of the DA transporter gene, with reciprocal downregulation of SERT. There were significant correlations between EtOH exposure and a) caspase-3 activation, b) reduced SERT protein levels, and c) reduced BDNF levels. SSRI exposure independently increased caspase-3 activity and downregulated SERT. Reduced SERT and BDNF levels were strongly correlated with reduction in eye diameter, a somatic manifestation of FASD. **Conclusion**: Maternal use of EtOH and SSRI during pregnancy each were associated with changes in fetal brain monoamine pathways that were consistent with potential mechanisms for the affective dysregulation associated with FASD.

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**Poster**

**PSTR003. ADHD, SLI, Dyslexia, and other Specific Disorders of Neurobehavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR003.10/B33

**Topic:** A.07. Developmental Disorders

**Support:** Korean Government Research Fund, Grant No. NRF-2022R1I1A3063177

**Title:** Cortisol-induced dysregulation of prenatal neuroendocrine impairs laong-term memory formation via delaying postsynaptic development in hippocampal CA1 neurons of rats

**Authors:** *S.-C. JUNG[1], **H.-J. KIM**[1], A. KHULAN[1], E.-A. KO[1], O.-B. KWON[2];
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**Abstract:** Previously, we reported that prenatal exposure to high cortisol induced attention deficit-hyperactivity disorder (ADHD)-like behaviors with cognitive deficits after weaning. In the present study, cellular mechanisms underlying cortisol-induced cognitive dysfunction were investigated using rat pups (Corti.Pups) born from rat mothers that were repetitively injected with corticosterone (s.c., 20 mg/kg /day, 21 days) during pregnancy. In results, Corti.Pups exhibited the failure of behavioral memory formation in the Morris water maze (MWM) test and the incomplete long-term potentiation (LTP) of hippocampal CA1 neurons. Additionally, glutamatergic excitatory postsynaptic currents (EPSCs) were remarkably suppressed in Corti.Pups compared to normal rat pups. Incomplete LTP and weaker EPSCs in Corti.Pups were attributed to the delayed postsynaptic development of CA1 neurons, showing a higher expression of NR2B subunits and lower expression of PSD-95 and BDNF. These results indicated that high cortisol might potently downregulate the BDNF-mediated signaling critical for the synaptic development of hippocampal CA1 neurons during brain development, and subsequently, induce learning and memory impairment. Our findings suggest a possibility that the prenatal dysregulation of cortisol triggers the epigenetic pathogenesis of neurodevelopmental psychiatric disorders, such as ADHD and autism.

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**Poster**

**PSTR003. ADHD, SLI, Dyslexia, and other Specific Disorders of Neurobehavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR003.11/B34

**Topic:** A.07. Developmental Disorders

**Support:** NIH Grant NEI R01EY023261

**Title:** Resting-state functional connectivity is altered in young adults with convergence insufficiency compared to binocularly normal controls

**Authors: *F. HAJEBRAHIMI**[1], S. GOHEL[1], M. SCHEIMAN[2], A. SANGOI[3], S. IRING-SANCHEZ,[3], C. MORALES-CARRASCO[4], E. SANTOS[5], T. ALVAREZ[3];
[1]Rutgers Univ., Newark, NJ; [2]Salus Univ., Elkins Park, PA; [3]New Jersey Inst. of Technol., Newark, NJ; [4]Univ. of Minnesota, Minneapolis, MN; [5]State Univ. of New York, New York City, NY

**Abstract:** This study sought to investigate the underlying resting-state functional connectivity (RSFC) in Convergence Insufficiency (CI) patients compared to binocularly normal controls (BNC) using functional Magnetic Resonance Imaging (fMRI) under The Convergence Insufficiency Neuro-mechanism Adult Population Study. A total of 101 participants were eligible for this study. After removing datasets with motion artifacts, 49 CI and 47 BNC resting-state fMRI datasets were analyzed. CI was diagnosed with the following signs: 1) receded near point of convergence (NPC) of greater than 6 cm, 2) reduced positive fusional vergence of less than 15Δ or failing Sheard's criteria of twice the near phoria, and 3) near phoria of at least 4Δ more exophoric compared to distance phoria and symptoms using the Convergence Insufficiency Symptom Survey (CISS) of greater than 21 points. RSFC was assessed using a group-level Independent Components Analysis (ICA) and Dual Regression. A behavioral correlation analysis was assessed using clinical measures and RSFC for both CI and BNC datasets. Results showed decreased RSFC within the Frontoparietal Network (FPN), Default Mode Network (DMN) and Visual Network (VN) in CI patients, compared to the BNC participants. The DMN RSFC strength was significantly correlated with the Positive Fusional Vergence (PFV), Near Point of Convergence (NPC), and the differences between the horizontal phoria at near compared to far (Diff-Phoria), but not to CISS. This study supports altered RSFC in CI patients compared to BNC participants and suggest these differences in underlying neurophysiology may in part lead to the differences in optometric visual function used to diagnose CI.

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**Poster**

**PSTR003. ADHD, SLI, Dyslexia, and other Specific Disorders of Neurobehavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR003.12/B35

**Topic:** A.07. Developmental Disorders

**Support:** NIH NICHD R15HD087937
Alan & Wendy Pesky Foundation Research Grant
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**Title:** Classification predictive modeling of dyslexia

**Authors:** Y.-C. YU[1], K. SHYNTASSOV[1], A. ZEWGE[2], ***L. A. GABEL**[3];
[1]Electrical and Computer Engin., Lafayette Col., Easton, PA; [2]Computer Sci., Lafayette Col., Lafayette College, PA; [3]Neurosci., Lafayette Col., Easton, PA

**Abstract:** Dyslexia is a reading disability that affects children across language orthographies, despite adequate intelligence and educational opportunity. If learning disabilities remain untreated, a child may experience long-term social and emotional problems, which may influence future success in all aspects of their lives. Early detection and intervention will help to close the gap between typically developing and reading impaired children in acquiring reading skills. We have demonstrated that animal models of dyslexia, genetic models based on candidate dyslexia susceptibility genes, and children with specific reading impairment show a common deficit on a virtual Hebb-Williams maze task. Since virtual maze task does not require oral reporting (rapid access to phonological processing) or rely on text, performance is not influenced by a potential difference in reading experience between groups. Although the correlation between dyslexia and the performance in the virtual Hebb-Williams maze task has been demonstrated, classification of atypical participants (i.e., dyslexic participants) through real-time observation of their performance on the virtual Hebb-Williams maze task is not feasible at this time. A computational model that can predict reading ability based on maze learning performance, would enable real-time feedback of the performance in the form of at-risk percentages for reading. Reading data and maze learning outcomes were analyzed from 227 school-aged children (8-14 years of age). Applying multiple variables (e.g. biological sex, age, time to complete the task, and deviation from the true path) into machine-learning based computational models resulted in prediction accuracy above 80%. Successful development of this predictive model would allow for early detection of risk for reading impairment, which can lead to early interventions to close the gap between typically developing and reading impaired children in acquiring reading skills.

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**Poster**

**PSTR003. ADHD, SLI, Dyslexia, and other Specific Disorders of Neurobehavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR003.13/B36

**Topic:** A.07. Developmental Disorders

**Title:** Early life stress induces sex-specific changes in behavior and parallel locus coeruleus neuron excitability

**Authors: *S. BRANNAN**[1], B. D. RICHARDSON[2], S. PORCAYO[3], J. BEAVERS[3]; [2]Southern Illinois Univ. - Sch. of Med., [1]Southern Illinois Univ. Sch. of M Pharmacol. & Neurosci. Grad. Program, Springfield, IL; [3]SIU Sch. of Med., Springfield, IL

**Abstract:** Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder with the core symptoms of hyperactivity, impulsivity, and inattention that tend to present differently in males and females. While males are more likely to present hyperactive and impulsive symptoms, inattention and stress-related comorbidities are more common in female patients. There is generally a higher prevalence of stress-related psychopathologies in females. Patients with post-traumatic stress disorder (PTSD) are four times more likely to develop ADHD, and stress has been shown to exacerbate ADHD symptoms. To identify a potential neurobiological basis for this relationship between stress, sex, and behavior, we first developed a dual-hit mouse model of early-life variable stress (ELVS) in C57bl/6J mice, administered during the postnatal period and late adolescence. Following ELVS exposure or daily handling (control), mice were evaluated for anxiety, attention, hyperactivity, and impulsivity. Preliminary data indicate that relative to control mice, female ELVS mice display hyperactivity and disrupted short-term memory, while there were no changes seen for these behaviors in male ELVS mice. Both male and female ELVS mice demonstrated reduced anxiety relative to control mice. Then, because neurons in the noradrenergic locus coeruleus (LC) are implicated in attention, arousal, and ADHD or related disorders, the electrophysiological properties of LC neurons were evaluated in male and female mice of both groups using whole-cell current-clamp electrophysiology. Female ELVS mice exhibited decreased spontaneous and evoked LC excitability in comparison to controls, while ELVS males displayed an opposing increase. These changes in excitability were decreased when steady state current injection was adjusted to maintain the membrane potential at -60 mV. Further analysis of the action potential maximum afterhyperpolarization (mAHP) amplitudes were also significantly increased in female ELVS mice compared to controls. Future studies will target this pathway to determine specific cellular mechanisms and subsets of cells that may be responsible for driving sex-specific behavioral changes. Using this novel animal model, we have identified sexual dimorphic changes in behavior that are paralleled by basal changes in LC neuronal activity. These results suggest that sexual dimorphism of the LC and its response to stress may lead to sex differences at the behavioral level. This indicates that sex and stress should be considered biological variables in specific drug treatments, particularly in ADHD and related disorders.

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**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.01/B37

**Topic:** A.07. Developmental Disorders

**Support:** 2020R1A2C2003268

**Title:** Akt and Ptf1a signaling regulates development of the GABAergic neurons in the cerebellum and risk for Schizophrenia

**Authors: *Y. BAE**[1], J.-Y. AHN[2];
[1]Sungkyunkwan Univ., Suwon, Korea, Republic of; [2]Mol. Cell Biol, Sungkyunkwan Univ. Sch. Med., Suwon, Kyonggi-do, Korea, Republic of

**Abstract:** AKT/PKB signaling plays a critical role in regulating cellular functions and is involved in neural development. However, the specific roles and molecular mechanisms of Akt signaling in the cerebellar development remain to be determined. Pancreas specific transcriptional factor 1a (PTF1A) is a transcription factor that is essential for driving neural precursors to differentiate into GABAergic neurons in the developing cerebellum. In this study, we identified that PTF1A is a new enzymatic substrate of AKT in developing cerebellum. AKT binds to PTF1A and phosphorylates it at Serine 154. Phosphorylation of PTF1A by AKT enhances its transcriptional activity toward Lhx1 and Lhx5 those are responsible for the generation of GABAergic neurons. Moreover, PTF1A phosphorylation by AKT copes it from ubiquitin-proteasomal system (UPS)-dependent degradation, reducing its interaction with FBXW7, rather caged in nucleus. Thus, our findings suggest that Akt signaling activates a bHLH transcription factor, PTF1A via phosphorylation, leading to induction of GABAergic neurons during cerebellar development.

**Disclosures: Y. Bae:** None. **J. Ahn:** None.

**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.02/B38

**Topic:** A.07. Developmental Disorders

**Support:** NIH Grant NS083513
AHA Predoctoral Fellowship 19PRE3480616

**Title:** Proinflammatory milieu disrupts homeostatic microglia-vascular interactions in the germinal matrix of prenatal human brain

**Authors:** J. CHEN[1], ***J. CHOI**[1], E. CROUCH[2], E. J. HUANG[3];
[2]Pediatrics, [3]Pathology, [1]Univ. of California, San Francisco, San Francisco, CA

**Abstract:** Premature births affect approximately 15 million infants worldwide each year. Among preterm infants born before 30 gestational weeks (GW), a significant portion (20-40%) develop germinal matrix hemorrhage (GMH), which leads to devastating neurodevelopmental sequelae with enormous socio-economic burdens. Despite its clinical significance, the underlying factors

contributing to the region-specific vulnerability of the germinal matrix remain unclear. The germinal matrix, also known as ganglionic eminences (GEs), of the prenatal human brain is known to harbor abundant neural stem and progenitor cells responsible for the development of GABAergic interneurons. Furthermore, this region exhibits robust angiogenesis driven by diverse endothelial and mural cells. Despite the immense interest in this area, there is a fundamental gap in our understanding of how immune cells regulate blood vessel formation and disruption in the GEs. The objective of this study is to investigate the role of the brain's innate immune cells in the regulation of angiogenesis and the susceptibility of blood vessels in the GEs to hemorrhage. We show that IBA1+ immune cells exhibit age-dependent interactions with nascent vasculature and are required for angiogenesis in GEs, but not cortical plates. Using single-cell transcriptomics and high dimensional flow cytometry, we identify distinct subsets of CD45+ immune cells that employ diverse signaling mechanisms to promote the formation of vascular networks in GEs in the prenatal human brain. Similar transcriptomic profiling of CD45+ cells from preterm infants with germinal matrix hemorrhage show that activated neutrophils and monocytes utilize a combination of bactericidal factors and chemokine CXCL16 to disrupt vascular integrity and promote hemorrhage in GEs. These results underscore the critical roles of the brain's innate immune cells in region-specific angiogenesis and how proinflammatory factors from these immune cells perturb this process, leading to GMH in preterm infants.

**Disclosures:** **J. Chen:** None. **J. Choi:** None. **E. Crouch:** None. **E.J. Huang:** None.

**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

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**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.03/B39

**Topic:** A.07. Developmental Disorders

**Support:** NSFC 81871079

**Title:** G3bp1/2 variants are associated with neurodevelopmental disorders and impair stress granule dynamics

**Authors:** ***B. DU**[1], X. JIA[2], S. TAN[3], H. GUO[4], K. XIA[5];
[1]Central South Univ., Chang Sha, China; [2]Central South Univ., Changsha, China; [3]Central South Univ., hunan, China; [4]central south university, hunan, China; [5]central south university, changsha, China

**Abstract:** Stress granules (SGs) are membrane-less compartments in eukaryotic cells that are dynamically induced by environmental stresses. G3BP1 and G3BP2 have the highest centrality within the core SG network and play a crucial role in SG assembly. However, their roles in neurodevelopment and neurodevelopmental disorders (NDDs) risk are not clear. By leveraging data from 40,853 individuals with NDDs, we found a nominally significant burden of de novo variants compared to random occurrence. Through GeneMatcher, we recruited five additional

NDD individuals with *de novo* missense variants in *G3BP1* or *G3BP2*. By generating *G3BP1* or *G3BP2* knockout cells and fluorescence recovery after photobleaching method, we found disorder-related *de novo* missense variants in *G3BP1/2* significantly suppressed the liquid-liquid phase separation and SG formation. Our findings implicate *G3BP1* and *G3BP2* are new NDD risk genes and suggest the SG pathology in NDDs. We are now generating *G3BP1* and *G3BP2* knock-in mouse to further investigate the underlying mechanisms.

**Disclosures: B. Du:** None. **X. Jia:** None. **S. tan:** None. **H. Guo:** None. **K. Xia:** None.

**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.04/B40

**Topic:** A.07. Developmental Disorders

**Title:** Pcm1 regulates posttranslational modifications of tubulin in the primary cilium

**Authors: *C. CHANG**, L. SAMENTAR, F. VANDERFORD, S. AKBAR, S. BOSS, M. GHANI, M. MOSHI, K. DHEDE, V. VO, E. OH;
Univ. of Nevada, Las Vegas, Las Vegas, NV

**Abstract:** The pericentriolar material 1 protein (PCM1) is a component of the centriolar satellites and regulates the biogenesis and function of the centrosome and cilium in the nervous system. In response to paracrine signaling, firing patterns in neurons are modified to accommodate changes in the cellular distribution of centriolar satellite proteins at the centrosome. Here, we demonstrate that unique PCM1 spliced isoforms are translated in specific cell lines and brain regions and that these protein isoforms are localized to discrete cellular compartments in neurons. Using mass spectrometry, we identified new protein networks that are complexed together with either the long or short PCM1 spliced isoforms. We also show how a long and a short isoform can coordinate post-translational modifications in tubulin in vitro and during the development of the brain. Electron tomography of synaptic terminals in the adult hippocampus highlight how PCM1 isoform products can modify the size and density of synaptic vesicles. Taken together, our data characterize a new role for centriolar satellite protein isoforms in the modification of tubulin and ciliogenesis.

**Disclosures: C. Chang:** None. **L. Samentar:** None. **F. Vanderford:** None. **S. Akbar:** None. **S. Boss:** None. **M. Ghani:** None. **M. Moshi:** None. **K. Dhede:** None. **V. Vo:** None. **E. Oh:** None.

**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.05/B41

**Topic:** A.07. Developmental Disorders

**Support:** Fonds de Recherche du Québec - Santé (FRQS)
Rare Diseases: Models & Mechanisms Network
Smith-Magenis syndrome Research Foundation

**Title:** Smith-magenis syndrome protein rai1 regulates body weight homeostasis through hypothalamic bdnf-producing neurons and trkb signalling

**Authors: *S. JAVED**[1], Y.-T. CHANG[2], Y. CHO[1], W.-H. HUANG[1], Y.-J. LEE[2], M. HAQUE[1]; [1]McGill Univ., Montreal, QC, Canada; [2]Ri-Muhc, Montreal, QC, Canada

**Abstract:** *Retinoic acid-induced 1* (*RAI1*) haploinsufficiency causes Smith-Magenis syndrome (SMS), a genetic disorder with symptoms including hyperphagia, hyperlipidemia, severe obesity, and autism phenotypes. Rai1 is a transcriptional regulator with a pan-neural expression pattern and hundreds of downstream targets. The mechanisms linking neural *Rai1* to body weight regulation remain unclear. Here we find that hypothalamic brain-derived neurotrophic factor (Bdnf)-TrkB signalling is disrupted in SMS ($Rai1^{+/-}$) mice. Selective Rai1 loss from all Bdnf-producing cells or from Bdnf-producing neurons in the paraventricular nucleus of the hypothalamus (PVH) induced obesity in mice. Electrophysiological recordings revealed that *Rai1* ablation increased inhibitory synaptic transmission to $PVH^{Bdnf}$ neurons and decreased intrinsic neuronal excitability. Chronic treatment of SMS mice with a partial agonist of tropomyosin receptor kinase B (TrkB), the cognate Bdnf receptor, delayed obesity onset. This treatment also partially rescued disrupted lipid profiles, insulin intolerance, and stereotypical repetitive behaviour in SMS mice. These data argue that Rai1 regulates body weight and metabolic function through hypothalamic Bdnf-producing neurons and that targeting TrkB signalling might improve associated SMS phenotypes.

**Disclosures: S. Javed:** None. **Y. Chang:** None. **Y. Cho:** None. **W. Huang:** None. **Y. Lee:** None. **M. Haque:** None.

**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.06/B42

**Topic:** A.07. Developmental Disorders

**Support:** Z01 ES100221

**Title:** Prenatal exposure to mineralocorticoid receptor antagonist spironolactone results in altered CA2 axonal projections and reactivity to novel objects

**Authors: *S. JONES**[1], S. J. SLEIMAN[1], G. M. ALEXANDER[1], P. N. SIEGLER[1,3], K. E. MCCANN[1], A. K. JARMUSCH[2], S. M. DUDEK[1];
[1]Neurobio. Lab., [2]Metabolomics Core Facility, NIEHS, Durham, NC; [3]Neurosci., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

**Abstract:** The spatiotemporal patterning of transcription factor expression has a well-appreciated role in the fate and function of many cell types. In the brain, hippocampal area CA2 is enriched with the Mineralocorticoid Receptor (MR; *Nr3c2*), a ligand-inducible transcription factor labile to stimulation by the stress hormone corticosterone. Recently, we discovered that MR is required for the acquisition and maintenance of the molecular, physiological, and behavioral features of CA2 by investigating embryonic and postnatal MR knockout mice. One curious contrast between these models was a disruption of hippocampal afferents from the supramammilary nucleus (SuM) in the embryonic, but not postnatal, model of MR loss. This result is suggestive of a specific role for MRs in establishing hippocampal neural connectivity during embryonic development. To test this assertion, we used a pharmacological model to perturb MR activity *in utero.* We implanted subcutaneous slow-release pellets containing the MR antagonist Spironolactone in dams during mid-gestation. In resulting litters, CA2 connectivity, CA2 molecular marker expression, and CA2-dependent behaviors were examined at adult ages. We assessed CA2 efferents to dorsal CA1 using a linear region-of-interest (ROI) through CA1 from alveus to stratum lacunosum-moleculare to capture signal intensity of fluorescently-labeled CA2 axons across CA1 layers in coronal sections. We found a significant main effect of treatment on fluorescence intensity across CA1 layers ($p<0.01$) that was due to Spironolactone treated animals having decreased fluorescence signal in CA1 stratum oriens, where CA2 axons preferentially project, relative to control animals. We assessed hippocampal afferents from SuM using immunohistochemical detection of the vesicular glutamate transporter 2 (vGluT2), which is expressed on SuM terminals. We found that vGluT2 fluorescent signal was significantly decreased in both CA2 ($p<0.01$) and dentate gyrus ($p<0.001$) in Spironolactone-treated animals. In contrast, we detected no significant effect of treatment on somatic stain for CA2 protein markers, suggesting that prenatal MR perturbation does not have lasting effects on CA2's distinct gene expression. Behaviorally, we found that Spironolactone-treated animals exhibited increased reactivity to novel objects ($p<0.05$), also in accordance with embryonic knockout of MR. However, we found no difference in preference for social novelty between the treatment groups. These findings suggest that developmental impairment in MR signaling, potentially mediated by maternal stress in early life, may have persistent effects on circuitry and behavior.

**Disclosures: S. Jones:** None. **S.J. Sleiman:** None. **G.M. Alexander:** None. **P.N. Siegler:** None. **K.E. McCann:** None. **A.K. Jarmusch:** None. **S.M. Dudek:** None.

**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.07/B43

**Topic:** A.07. Developmental Disorders

**Support:** NIH K08 NS119797-01A1
Harold Amos Medical Faculty Development Program

**Title:** Disruption of single-nucleus multimodal dynamics predicts persistent dysfunction in glutamatergic neurons after prenatal hypoxia

**Authors: *A. G. CRISTANCHO**[1], D. JOSEPH[2], M. CASSIDY[1], P. CHAUHAN[1], E. GADRA[1], E. GADRA[1], D. ZARRINNEGAR[1], B. RODRIGUEZ[1], E. MARSH[3];
[1]Neurol., [2]Dept. of Neurol., Children's Hosp. of Philadelphia, Philadelphia, PA; [3]Div. Child Neurol, Childrens Hosp. of Philadelphia, Philadelphia, PA

**Abstract:** Prenatal and perinatal hypoxic injury affects over a million births annually, eventually leading to neurodevelopmental disability in one-third of those children. Yet, we lack targeted interventions for improving outcomes. A limitation toward developing therapeutics is that we lack understanding of the multifaceted, cell type-specific molecular consequences of this transient insult on the developing brain. To address this gap, we performed joint single nucleus RNA-sequencing and assay for transposase-accessible chromatin sequencing from the cortex of mice immediately after prenatal hypoxia exposure (8 hours of 5% inspired oxygen at embryonic day 17.5). This animal model phenocopies mild hypoxic injury seen in neonatal children. Over 140,000 nuclei were sequenced from 16 total samples evenly divided between normoxia and hypoxia as well as males and females. We identified clusters of known neuronal and glial cell populations. Prenatal hypoxia led to a slight increase in endothelial cells but no further changes in cell number for other cell types. Genes that were dysregulated by hypoxia in all cell types were enriched for pathways related to metabolism and RNA splicing and processing. RNA splicing-related gene dysregulation was associated with global disruption of RNA velocity, the single cell ratio of unspliced to spliced transcripts. Furthermore, we found several cell type-specific disruptions in gene expression and regions of chromatin organization after prenatal hypoxia. Most remarkably, we discovered that hypoxic glutamatergic neurons had a selective disassociation between global chromatin organization and gene expression. Glutamatergic neurons, which develop synapses postnatally, also demonstrated dysregulation of genes associated with neuron structure and function after prenatal hypoxia. To test whether these changes in the fetal brain suggested which cells and pathways may be disrupted by hypoxia in mature neurons, we used Golgi staining and whole-cell patch-clamp electrophysiology in juvenile mice to examine their structure and function. We found that glutamatergic neurons had decreased dendritic spine density and disruptions in excitability and one month after the hypoxic insult. Many of the potassium channels associated with hyperpolarization were not expressed in fetal glutamatergic neurons at baseline, but about 80% of these genes had abnormalities in nearby chromatin accessibility after prenatal hypoxia. Together, these findings suggest that prenatal hypoxia disrupts the organization of chromatin and the transcriptome in glutamatergic neurons, leading to persistent disruption of neuronal maturation and structure.

**Disclosures: A.G. Cristancho:** None. **D. Joseph:** None. **M. Cassidy:** None. **P. Chauhan:** None. **E. Gadra:** None. **E. Gadra:** None. **D. Zarrinnegar:** None. **B. Rodriguez:** None. **E. Marsh:** None.

**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.08/B44

**Topic:** A.07. Developmental Disorders

**Title:** Exploring the role of schizophrenia associated genes in neuronal remodeling

**Authors: *S. KERET**, O. SCHULDINER;
Weizmann Inst. of Sci., Rehovot, Israel

**Abstract:** The wiring of the adult nervous system underlies its correct function. Its precise connectivity is shaped during early and postnatal developmental. Collectively known as developmental neuronal remodeling, these postnatal processes include neurite pruning often followed by regrowth as a conserved strategy to refine neural circuits in both vertebrates and invertebrates. Impairments in neuronal remodeling were implicated for a long time in a wide variety of neuropsychiatric disorders such as Autism Spectrum Disorder and Schizophrenia (SCZ). However, the mechanisms by which remodeling leads to neuropsychiatric disorders are still mostly unclear. Specifically, we aim to address this gap by understanding the link between impairments in neuronal remodeling to SCZ. SCZ is a neuropsychiatric disorder that affects ~1% of the population worldwide, and yet its causes (genetic, developmental, environmental), mechanism of action, and treatments mechanisms are not well understood. SCZ patients experience positive symptoms that refer to delusions and hallucinations (i.e. additive experiences, hence the term positive symptoms) along with negative symptoms such as anhedonia and more (i.e. lack of normal functions). It is known from MRI studies that SCZ patients experience loss of grey and white matter already at the onset of the disease compared to healthy subjects. This was hypothesized by I. Feinberg 1982, to occur by over-pruning occurring during developmental neuronal remodeling. We aim to find a link between common Single Nucleotide Polymorphism (SNP) among SCZ patients and neuronal remodeling during development. Using the stereotypic remodeling of the *Drosophila* mushroom body (MB), required for learning and memory mostly of olfactory stimuli, I screened 39 fly genes which are orthologues of genes containing SNPs in SCZ GWAS studies. Using RNAi to knockdown each of these genes within the MB- γ neurons I found that 11 genes-knockdown result in abnormal MB phenotype. At this point I am further exploring these candidates.

**Disclosures: S. Keret:** None. **O. Schuldiner:** None.

**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.09/B45

**Topic:** A.07. Developmental Disorders

**Support:** ICTR Voucher Program, University of Maryland Baltimore

**Title:** TANC2 does not modulate mTOR pathway signaling or impact neuronal morphology

**Authors: *E. A. PATTIE**[1,2], J. A. EINHORN[3], R. D. MCNAIR[1], S. NUSRATY[3], P. H. IFFLAND, II[2];
[1]Univ. of Maryland Sch. of Med. Program In Neurosci., Baltimore, MD; [2]Dept. of Neurol., Univ. of Maryland Sch. of Med., Baltimore, MD; [3]Univ. of Maryland Col. Park, College Park, MD

**Abstract:** Genetic variants in the TANC2 gene are associated with a range of neurodevelopmental disorders including autism spectrum disorder, intellectual disability, and developmental delays. In addition, variants in TANC2 have been associated with Lennox-Gastaut Syndrome, a severe form of epilepsy with childhood onset that is often accompanied by treatment resistant epilepsy. Despite the known clinical implications of TANC2 variants, its mechanistic role in the brain in health and disease remains unclear. In rodents, TANC2 is highly expressed throughout the brain during development and TANC2 deficiencies are embryonically lethal. Previous studies have also linked TANC2 to a variety of roles ranging from synaptic scaffolding at dendritic spines to inhibiting mTOR signaling. To further explore the role of TANC2 in neuronal cell signaling and brain development, we developed in vitro CRISPR/Cas9 knockout models of TANC2 deficiency and a TANC2 overexpression cell line by transfection into neuron-like mouse Neuro-2a and human SK-N-SH cells, with and without differentiation by retinoic acid. We hypothesized that overexpression of TANC2 would inhibit mTOR pathway signaling and that knocking out TANC2 would result in mTOR pathway hyperactivation. We observed no changes in mTOR pathway signaling after TANC2 KO, as measured by Western blot of PS6 (Ser240/244) and P4E-BP1 (Thr37/46). In addition, there was also no effect on dendrite outgrowth or soma size (both hallmarks of mTOR pathway hyperactivation). Lastly, overexpressing TANC2 in N2a cells did not result in mTOR pathway inhibition. Based on these findings, TANC2 does not play a regulatory role in mTOR signaling but may play a role in alternative cell signaling cascades that modulate developmental processes in the brain. Further work is necessary to elucidate the mechanistic role of TANC2 and how its genetic variants play a role in neurodevelopmental disorders.

**Disclosures: E.A. Pattie:** None. **J.A. Einhorn:** None. **R.D. McNair:** None. **S. Nusraty:** None. **P.H. Iffland:** None.

**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.10/B46

**Topic:** A.07. Developmental Disorders

**Support:** NIH Grant R01NS112642

**Title:** Endoplasmic reticulum chaperone, bip protects microglial cells from endoplasmic reticulum stress mediated apoptosis under hyperglycemic conditions

**Authors: *W. ANTONISAMY**, G. BAHADER, Z. SHAH;
Medicinal and Biol. Chem., Univ. of Toledo, Toledo, OH

**Abstract: Background:** Binding of Immunoglobulin heavy chain protein (BIP) is a major endoplasmic reticulum (ER) chaperone facilitating the assembly of newly synthesized proteins in the ER. Microglial cells vigorously respond to brain injuries and eliminate the damaged neuronal and apoptotic cells through phagocytosis in the central nervous system. However, hyperglycemia's mechanism of BIP-mediated microglial cell function is unclear. We explored the molecular mechanism of BIP in microglial function during hyperglycemia conditions.
**Methods:** Hyperglycemia was induced in C57BL/6J mice by two consecutive intraperitoneal injections of streptozotocin (STZ 100/kg) and confirmed by measuring the blood glucose from day 2 to day 14. After 14 days of experimental condition, mice were sacrificed, brains were collected, and tissue lysate was prepared for ER chaperone studies. In-vitro hyperglycemia was induced by exposing HMC3 cells to 25mM glucose for 5 days and proteins involved in ER stress, apoptosis, and autophagy were analyzed.
**Results:** In hyperglycemic conditions, the major ER chaperone BIP protein expression was dramatically reduced in HMC3 cells, which led to increased apoptosis through the activation of CHOP and mitochondrial pro-apoptotic proteins (Bax, Bad, cleaved caspase-3). The flow cytometry results also indicate hyperglycemia-induced apoptosis and reactive oxygen species (ROS) production. Interestingly, the BIP inducer X restored the apoptosis in microglia through the de-repression of BIP and inhibition of ER stress. These results suggest that the ER chaperone BIP is required for the microglial function and protects from apoptosis in hyperglycemia. A better understanding of the molecular mechanisms and the role of BIP in microglia function may contribute to developing novel therapies for microglia dysfunction-associated neurodegenerative diseases.

**Disclosures: W. Antonisamy:** None. **G. Bahader:** None. **Z. Shah:** None.

**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.11/B47

**Topic:** A.07. Developmental Disorders

**Title:** Cohen-syndrome associated VPS13B regulates mitochondrial morphology

**Authors: *S.-K. LEE**[1], H.-J. HAM[1], J. MUN[2], D.-J. JANG[3], J.-A. LEE[1];
[1]Dept. of Biol. Sci. and Biotech., Hannam Univ., Daejeon, Korea, Republic of; [2]Dept. of Structure & Function of Neural Network, Korea Brain Res. Inst. (KBRI), Daegu, Korea,

Republic of; [3]Kyungpook Natl. Univ., Kyungpook Natl. Univ., Sangju-si/gyeongsangbuk-Do, Korea, Republic of

**Abstract:** The Vacuolar Protein Sorting 13 Homolog B (VPS13B) is a large transmembrane protein that is associated with Cohen syndrome (CS), a neurodevelopmental disorder. However, its precise function and cellular pathogenic mechanism are not fully understood. In this study, we found that the loss of VPS13B resulted in abnormalities in both mitochondrial morphology and function. Our analysis using electron microscopy and immunostaining revealed that VPS13B KO cells have enlarged mitochondria, which results in impaired membrane potential, and dynamics of mitochondria, compared to WT. Interestingly, our transcriptomic analysis showed that mitochondria associated genes are dysregulated. Indeed, mRNA expression levels of DCN (Decorin), a mitophagy associated proteoglycan, and Mfn2(mitofusin2), a key player in mitochondria fusion, were significantly reduced in VPS13B KO cells. Moreover, mitochondrial proteins such as TIM23, ubiquitinated parkin or PINK1 accumulated in VPS13B KO cells. Mitophagy flux was also impaired, leading to accumulation of damaged mitochondria in VPS13B KO cells. More intriguingly, CS iPSC(induced pluripotent stem cell)-derived neurons have larger mitochondria, a reduced mitochondria membrane potential, an accumulation of PINK1 protein, and reduced Drp1 protein level compared to control neurons. Taken together, we provide novel roles of VPS13B on regulation of mitochondria and a new pathogenic mechanism of CS associated with mitochondrial dysfunction.

**Disclosures:** **S. Lee:** None. **H. Ham:** None. **J. Mun:** None. **D. Jang:** None. **J. Lee:** None.

**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.12/B48

**Topic:** A.07. Developmental Disorders

**Support:** RO1NS131223
AES Junior Investigator Award
AES BRIDGE award

**Title:** Nprl2 knockout results in altered neuronal morphology in vitro and laminar disorganization in vivo

**Authors: *S. BRUCKMEIER**[1], D. KOLB[3], K. ROARK[1], P. H. IFFLAND[2];
[1]Neurol., [2]Univ. of Maryland Sch. of Med., Univ. of Maryland Sch. of Med., Baltimore, MD;
[3]Univ. of Maryland, College Park, MD

**Abstract:** Malformations of cortical development (MCD) are a common cause of medically refractory epilepsy. The most common type of drug-resistant epilepsy in children results from focal cortical dysplasia (FCD type 2; FCD2), a type of MCD. FCD2 is most commonly caused by variants in genes that encode proteins forming the GATOR1 complex (NPRL3, DEPDC5, and

NPRL2)- a negative regulator of the mTOR pathway. FCD2 phenotypes such as abnormal neuron morphology and cortical dysplasia are linked to mTOR hyperactivation. While *NPRL3* and *DEPDC5* variants are well defined, *NPRL2* variants are emerging as another frequent cause of FCD2. We hypothesize that *Nprl2* KO will result in mTOR-dependent alterations in neuronal morphology *in vitro* and cortical dyslamination *in vivo*. An *Nprl2* KO line was generated by targeting exon 5 of *Nprl2* via CRISPR/Cas9 in mouse Neuro2a cells (N2aC). N2aC WT, scramble control (SC), and KO cells were treated with mTOR inhibitors (rapamycin and torin1) or treated with amino acid-free media to assess phosphorylated ribosomal S6 levels or LAMP2/mTORC1 co-localization. Cell lines were treated with vehicle or mTOR inhibitors and visualized via immunofluorescence staining with F-actin to measure soma size. Time-lapse imaging was used to capture aggregation patterns in each cell line with or without mTOR inhibitors. Cell size and process outgrowth was assayed via F-actin or MAP2 probing and spinning disk confocal microscopy. CD1 mouse embryos underwent *in utero* electroporation (IUE) using *Nprl2* CRISPR/Cas9 or scramble plasmids at E14. Dams were injected with rapamycin 24 hrs after surgery. At P3, brains were dissected from IUE pups and processed by immunohistochemistry using primary antibodies recognizing GFP, SATB2 (layer II/III), and CTIP2 (layer IV-VI) and then secondary antibodies. Brain sections were imaged on a Keyence microscope and analyzed by binning images into cortical layers I,-III, IV-VI, and white matter zones. *Nprl2* KO resulted in mTOR-dependent increases in pS6. KO cells also showed mTOR-dependent increases in soma size and process outgrowth vs. WT cells. Additionally, KO cells showed inappropriate localization of mTORC1 to the lysosome during amino acid starvation and formed abnormal aggregates compared to control cells. Further, there were a greater number of cells in each aggregate in the KO cell line. *Nprl2* IUE mice displayed GFP-positive heterotopic neurons in the sub-cortical white matter while Scram IUE neurons displayed GFP+ cells only in layer II and III. *Nprl2* KO results in mTOR hyperactivation, altered morphology, inappropriate localization of mTORC1 to the lysosome, and cortical dyslamination which is consistent with FCD phenotypes.

**Disclosures:** **S. Bruckmeier:** None. **D. Kolb:** None. **K. Roark:** None. **P.H. Iffland:** None.

**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.13/B49

**Topic:** A.07. Developmental Disorders

**Support:** NRF-2022R1A2C1002925
NRF-2017R1A5A1015366

**Title:** Neuronal Modeling of DNM1L Mutations: Unveiling the Mechanisms Underlying Clinical Severity

**Authors: *K. SO**, S. BAEK;
POSTECH, Pohang-si, Korea, Republic of

**Abstract:** *DNM1L*, a gene encoding the Drp1 protein involved in mitochondria and peroxisomes division, has been associated with a spectrum of clinical symptoms ranging from mild optic atrophy to severe epileptic encephalopathy. However, the functional implications of different *DNM1L* mutations, particularly in the symptom-related neurological context, remain poorly understood. In this study, we employed neuronal models to investigate the effects of *DNM1L* mutations associated with varying clinical severities. We introduced vectors containing each DNM1L mutation into developing mouse brains via *in-utero* electroporation. Overexpression of mutations associated with mild symptoms resulted in postnatal migration defects, while mutations associated with severe symptoms caused reductions in cell number, axon branching, and dysgenesis of the corpus callosum. Notably, the phenotypic differences were not attributed to abnormalities in prenatal apoptosis or proliferation, but rather emerged during the early postnatal stage, suggesting a distinct stage-specific mechanism for severe symptom-related variants. Furthermore, using *DNM1L* Tet-Off human neural progenitor cell lines with the knockout of the endogenous allele, we characterized the differential impact of mutations on organelle dynamics. Our findings provide valuable insights into the symptom-related functional consequences of *DNM1L* mutations and their clinical implications in neurodevelopmental disorders.

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

**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.14

**Topic:** A.07. Developmental Disorders

**Support:** NIH RO1 (5R01MH129732-02, A-CM)

**Title:** A non-canonical mechanism of Complement 4-mediated cortical synaptic loss

**Authors: *R. PHADKE**[1], E. KRUZICH[2], L. FOURNIER[2], A. BRACK[1], M. SHA[2], I. PICARD[3], A. COMER[3], C. JOHNSON[3], D. STROUMBAKIS[3], M. SALGADO[3], Y. LIU[3], A. CRUZ-MARTIN[1];
[1]Mol. and Cell. Biol. and Biochem., [2]Neurobio., [3]Boston Univ., Boston, MA

**Abstract:** The function of the immune complement (C) pathway embodies neuroimmune adaptations, playing a pivotal role in synaptic plasticity. In fact, disruptions in the C pathway have been linked to devastating brain diseases exhibiting pathological synaptic loss, such as schizophrenia (SCZ) and Alzheimer's disease. Our group previously demonstrated that increasing the levels of the SCZ risk gene, complement component 4 (*C4*) – a member of the immune complement cascade – leads to hypoconnectivity of developing cortical neurons. A

long-standing dogma in the neuro-immune field is that cells in the brain can release complement proteins into the extracellular space, where they modify the connectivity of neurons through the activity of the complement receptor 3 (CR3) and the recruitment of microglia. However, our preliminary data show that overexpression of C4 (C4-OE) via *in utero* electroporation (IUE) in transgenic mice lacking the CR3 leads to a decrease in the density of postsynaptic dendritic spines of layer (L) 2/3 PFC pyramidal neurons compared to controls, suggesting that C4 acts through an independent, non-canonical mechanism. Using co-immunoprecipitation in HEK293T cells, we show that C4 interacts with Sorting Nexin 27 (SNX27), an endosomal protein. Importantly, IUE of both C4 and SNX27 leads to an increase in the density of dendritic spines and rescue of the miniature excitatory postsynaptic current frequency of L2/3 PFC neurons, undistinguishable from that of controls, indicating that increased levels of SNX27 could rescue C4-induced hypoconnectivity. Using STED super-resolution microscopy in brain slices, we demonstrate that C4-OE leads to a reduced amount of AMPA receptor subunit GluR1 in Rab11a-positive recycling endosomes while increasing the amount of subunit in the Lamp1-positive lysosomes in dendritic spines in L1 apical tufts, a circuit implicated in controlling states of consciousness, attention, and learning. We also demonstrate that C4 is colocalized with SNX27 nanoclusters in dendritic spines, suggesting that this immune molecule is associated with the intracellular endosomal machinery. Overall, we show that in the dendritic spines of PFC neurons, C4 disrupts the function of SNX27, which leads to dysregulation of the endosomal machinery, increased degradation of GluR1, and decreased connectivity. Our new model provides one of the first pieces of evidence of neuron-autonomous mechanisms of complement-dependent synaptic weakening and suggests that synaptic engulfment by microglia might be a consequence of neuronal synaptic plasticity.

**Disclosures:** **R. Phadke:** None. **E. Kruzich:** None. **L. Fournier:** None. **A. Brack:** None. **M. Sha:** None. **I. Picard:** None. **A. Comer:** None. **C. Johnson:** None. **D. Stroumbakis:** None. **M. Salgado:** None. **Y. Liu:** None. **A. Cruz-Martin:** A. Employment/Salary (full or part-time); Neurobiology Section in the Department of Biology, Boston University, Boston, MA, USA, Center for Systems Neuroscience, Boston University, Boston, MA, USA, The Center for Network Systems Biology, Boston University, Boston, MA, USA, Department of Pharmacology and Experimental Therapeutics, Boston University, Boston, MA, USA.

**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.15

**Topic:** A.07. Developmental Disorders

**Support:** NIH/NIMH R01 MH127081-01A1

**Title:** Investigating the molecular signatures of ASH1L ASD mutations in human iPSC-derived neurons.

**Authors: *C. S. LEUNG**[1], J. A. WARD[1], F. D. RITCHIE[2], S. BERTO[3], V. G. CORCES[4], J. S. LIU[1], S. B. LIZARRAGA[1];
[1]Dept. of Mol. Biology, Cell Biol. and Biochem., Brown Univ., Providence, RI; [2]Dept. of Biol. Sci., Univ. of South Carolina, Columbia, SC; [3]Dept. of Neurosci., Med. Univ. of South Carolina, Charleston, SC; [4]Dept. of Human Genet., Emory Univ. Sch. of Med., Atlanta, GA

**Abstract:** Autism spectrum disorder (ASD) is characterized by impairments in social communication and social interactions as well as the presence of restrictive and repetitive behaviors. Chromatin and transcriptional regulators are among the class of genes most commonly mutated in ASD. Absent, Small, Or Homeotic-Like (ASH1L) is a major genetic risk factor for ASD, and it encodes for a histone methyltransferase that deposits two methyl groups on lysine 36 on histone H3 (H3K36me2). Previous work from our lab suggests that ASH1L modulates molecular mechanisms governing neuronal morphogenesis. However, the molecular signatures that are regulated by ASH1L in human neuronal development are unknown. Here, we generated disease variants in ASH1L that are associated with a range of phenotypes including ASD, seizures and with variable degrees of intellectual disability (ID). We used genome editing to generate nonsense pathogenic mutations in the chromatin binding domain (R2426*) and the catalytic domain (E2143*) of ASH1L in human induced pluripotent stem cells (iPSCs) from a neurotypical male individual. Through bulk RNA-sequencing (RNA-seq) of iPSC-derived cortical excitatory neurons containing the ASH1L mutations, we observed widespread dysregulation of multiple gene expression programs. In addition to changes in gene expression, we also observed extensive differential isoform usage and alternative splicing changes in the ASH1L mutants. Lastly, we performed chromatin immunoprecipitation approaches followed by sequencing or CUT&TAG to determine how levels and positioning of specific histone modifications are altered in the ASH1L mutant iPSC-derived neurons. Integration of the transcriptomic and epigenomic datasets in this study will allow us to uncover the molecular underpinnings associated with ASH1L dysfunction in human neurons.

**Disclosures: C.S. Leung:** None. **J.A. Ward:** None. **F.D. Ritchie:** None. **S. Berto:** None. **V.G. Corces:** None. **J.S. Liu:** None. **S.B. lizarraga:** None.

**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.16/B50

**Topic:** A.07. Developmental Disorders

**Support:** Medical Research Council grant (MR/S037667/1)

**Title:** Erk signalling in the neurodevelopmental disorders associated with 16p11.2 copy number variations

**Authors: *I. MORELLA**[1], F. BEDOGNI[2], M. FJODOROVA[1], C. BUTTER[3], C. GOLDIE[3], J. HALL[1], O. SQUIRE[1], C. ZUGLIAN[4], J. GREEN[3], M. LI[1], K. SHARMA[5], M. VAN DEN BREE[1], R. BRAMBILLA[1];
[2]Sch. of Med., [1]Cardiff Univ., Cardiff, United Kingdom; [3]The Univ. of Manchester, Manchester, United Kingdom; [4]Univ. di Pavia, Pavia, Italy; [5]Manchester Univ. NHS Fndn. Trust, Manchester, United Kingdom

**Abstract:** Copy number variations (CNVs) at the chromosomal region 16p11.2 are associated with autism spectrum disorder, intellectual disability and other neurodevelopmental disorders (NDDs). Converging evidence from mouse models and human studies points to MAPK3, a gene located in the 16p11.2 region, as a key factor for NDD. MAPK3 encodes for ERK1, a protein kinase of ERK signalling cascade, which regulates neurodevelopment, cognition and behavioural plasticity. Moreover, recent data suggest that dysfunctions in the cortico-striatal connectivity underlie NDDs in both patients affected by NDDs and mouse models of 16p11.2 deletion. To better elucidate the role of ERK signalling in the pathophysiology of NDDs associated with 16p11.2 CNVs, we employed both mouse models of 16p11.2 CNVs and human iPSCs-derived neurons. In addition, human carriers of 16p11.2 deletion and duplication were screened for peripheral alterations of ERK signalling components.Our data demonstrate that MAPK3/ERK1 genetic alterations are reflected in corresponding biochemical changes in blood samples human 16p11.2 deletion and duplication patients.In addition, converging evidence from our mouse models and iPSCs-derived neurons points to a potential dysregulation of dopaminergic signalling in 16p11.2 CNVs. Altogether, our results suggest that peripheral signalling intermediates may become reliable biomarkers for NDDs. Moreover, the 16p11.2 CNVs may be implicated in cortico-striatal dysfunctions underlying NDDs.

**Disclosures: I. Morella:** None. **F. Bedogni:** None. **M. Fjodorova:** None. **C. Butter:** None. **C. Goldie:** None. **J. Hall:** None. **O. Squire:** None. **C. Zuglian:** None. **J. Green:** None. **M. Li:** None. **K. Sharma:** None. **M. Van den Bree:** None. **R. Brambilla:** None.

**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.17/B51

**Topic:** A.07. Developmental Disorders

**Support:** Merck & Co

**Title:** Behavioral and metabolic consequences of the LINE-1 transposition into murine thyroglobulin gene of C57BL/6NTac mice

**Authors: *T. ROSAHL**[1], W. BAILEY[2], B. SMITS[4], Z. ERDOS[2], J. GASPAR[3], S. KURUVILLA[2], P. LANE[2], D. THUDIUM[2], M. MACGOWAN[4], H. MULTARI[4], C. CUMO[4], A. NAVIS[4], E. LAGHOUATI[5], F. RIET[5], B. PETIT-DEMOULIERE[5], B. PETIT-DEMOULIERE[5],

M. SELLOUM[5], H. JACOBS[5], G. BOU ABOUT[5], T. FOREST[2];
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**Abstract:** A naturally occurring spontaneous mutation was discovered in Taconic Biosciences' wildtype C57BL/6NTac mice that is strongly associated with early-onset thyroid dysplasia. Whole genome sequencing of affected vs unaffected animals revealed that the genetic variant was caused by transposition of a L1 long interspersed nuclear element (LINE) which inserted into an intron within the Thyroglobulin (Tg) gene. The presence of the LINE-1 interferes with splicing, resulting in exon 26 to be excluded from most Tg transcripts as shown by RNAseq analysis of the thyroid transcriptome of homozygous animals. The resulting phenotype is inherited in an autosomal dominant manner with affected mice exhibiting thyroid follicular cell dysplasia that progressed to thyroid adenoma by 12 months of age with incomplete penetrance. Here, we studied the functional consequences of the LINE-1 transposition by running Wild-type, Heterozygous and Homozygous C57BL/6NTac males for that mutation through a battery of behavioral and metabolic tests. The behavioral tests included circadian activity, open field, SHIRPA, grip strength, rotarod, fear conditioning and formalin pain test. The metabolic cohort consisted of blood chemistry, electrocardiogram, Echocardiography, Oral Glucose Tolerance Test and energy expenditure upon 10-week treatment with a GAN NASH diet. The results will be presented at the meeting.

**Disclosures:** **T. Rosahl:** A. Employment/Salary (full or part-time); Merck & Co. **W. Bailey:** A. Employment/Salary (full or part-time); Merck & Co. **B. Smits:** A. Employment/Salary (full or part-time); Taconic Biosciences. **Z. Erdos:** A. Employment/Salary (full or part-time); Merck & Co. **J. Gaspar:** A. Employment/Salary (full or part-time); Merck & Co. **S. Kuruvilla:** A. Employment/Salary (full or part-time); Merck & Co. **P. Lane:** A. Employment/Salary (full or part-time); Merck & Co. **D. Thudium:** A. Employment/Salary (full or part-time); Merck & Co. **M. MacGowan:** A. Employment/Salary (full or part-time); Taconic Biosciences. **H. Multari:** A. Employment/Salary (full or part-time); Taconic Biosciences. **C. Cumo:** A. Employment/Salary (full or part-time); Taconic Biosciences. **A. Navis:** A. Employment/Salary (full or part-time); Taconic Biosciences. **E. Laghouati:** A. Employment/Salary (full or part-time); ICS. **F. Riet:** A. Employment/Salary (full or part-time); ICS. **B. Petit-Demouliere:** A. Employment/Salary (full or part-time); ICS. **B. Petit-Demouliere:** A. Employment/Salary (full or part-time); ICS. **M. Selloum:** A. Employment/Salary (full or part-time); ICS. **H. Jacobs:** A. Employment/Salary (full or part-time); ICS. **G. Bou About:** A. Employment/Salary (full or part-time); ICS. **T. Forest:** A. Employment/Salary (full or part-time); Merck & Co.

**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.18/B52

**Topic:** A.07. Developmental Disorders

**Support:** Lieber Institute for Brain Development
NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation
National Institute of Health (NIH) T32 Fellowship
Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) - Financing code 001
FAPESP - Sao Paulo Research Foundation (http://www.fapesp.br/en/): Grant Number 2018/18560-6
CFAR: P30AI094189-04

**Title:** Making a human specific model: Maternal Immune Activation and Neuroinflammation

**Authors: *B. SPIEGELBERG**[1,2], E. TIETZE[2], A. R. BARBOSA[2], B. H. S. ARAUJO[2], V. EUCLYDES[2], T. SAWADA[2], H. CHO[2], Y. LEE[2], A. FELTRIN[2], J. VAN DE LEEMPUT[2], K. J. BENJAMIN[2], H. BRENTANI[2], D. R. WEINBERGER[2], R. MCKAY[2], J. SHIN[2], A. C. M. PAQUOLA[2], J. ERWIN[2,1];
[1]Johns Hopkins Med. Institutions, Baltimore, MD; [2]Lieber Inst. For Brain Develop., Baltimore, MD

**Abstract:** The human placenta is essential for the development and survival of a developing fetus. It is the main communicator between fetus and mother and is responsible for producing hormones and growth factors for correct fetal development during pregnancy. Maternal Immune Activation (MIA) plays a role in antagonizing the placenta and increasing risk of neurodevelopmental disorders, by causing a proinflammatory state. This information is known from human epidemiological studies and animal models, but the human placenta is severely understudied. There is a gap in the scientific field for a human specific placenta model to better understand the interplay of MIA and neurodevelopmental disorders. Primary human trophoblast stem cells (hTSC) and human pluripotent stem cells (hPSC) differentiated to hTSC can potentially model placental processes *in vitro*. Yet, it remains controversial how the differentiation of human pluripotent stem cells to trophectoderm relates to *in vivo* development and the factors required for this differentiation. Here, we demonstrate that the primed pluripotent state retains potency to generate trophoblast stem cells by activating EGF and WNT and inhibiting TGFb, HDAC and ROCK signaling without exogenous BMP4 (named TS). We map this specification by temporal single cell RNAseq compared to activating BMP4 or activating BMP4 and inhibiting WNT. TS conditions generate a stable proliferating cell type that is highly similar to six-week placental cytotrophoblasts with activation of endogenous retroviral genes and without amnion expression. Multiple primed iPSC and ES lines differentiate to iPS-derived-TSCs that can be passaged for at least 30 passages and differentiate to pure populations of multinucleated syncytiotrophoblasts (STB) and extravillous trophoblast cells. Having establish that primed IPSC and ES lines can be used to make an in vivo model of TSC, we were able to use this to create a model to study MIA and neuroinflammation with, specifically, STB as the mediator. We show that by exposing STBs to a RNA viral analog, they produce proinflammatory cytokines, mimicking MIA.

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**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.19/B53

**Topic:** A.07. Developmental Disorders

**Support:** NIH Grant R01NS131620
USC-Buck Nathan Shock Center P30AG068345
NSF Graduate Research Fellowship

**Title:** Investigating the molecular basis of RNA exosome-linked neurodevelopmental disorders

**Authors: *L. HIGGINSON**, M. TORSTRICK, N. ELIAS, J. BURFORD, D. J. MORTON; USC, Los Angeles, CA

**Abstract:** Post-transcriptional regulation of gene expression is critical for proper neuronal development and function. Many of these highly coordinated post-transcriptional regulatory events are mediated by an evolutionarily conserved and ubiquitously expressed RNA processing complex, the RNA exosome. Recent clinical reports have linked autosomal recessive missense mutations in the genes encoding structural subunits of the RNA exosome to distinct tissue-specific disorders with shared neurological features. Disease-linked mutations in RNA exosome subunit genes: *EXOSC3* and *EXOSC9* cause distinct subtypes of a devastating neurodevelopmental disorder, Pontocerebellar Hypoplasia. In contrast, mutations in RNA exosome subunit gene *EXOSC2* cause a novel syndrome, SHRF (**S**hort stature, **H**earing loss, **R**etinitis pigmentosa, and distinctive **F**acies), with mild cerebellar atrophy. These observations indicate tissue-specific function for the RNA exosome and an enhanced requirement for the complex in neurodevelopment. Towards understanding the biological mechanism of RNA exosome-linked neuronal dysfunction, my studies will focus on systematically investigating and comparing the cell type/tissue-specificity of pathogenic variants in distinct RNA exosome subunits in the fly brain. Thus, I have engineered flies modeling pathogenic mutations in RNA exosome Cap subunit genes: EXOSC2 (fly Rrp4), EXOSC3 (fly Rrp40), and Core subunit gene EXOSC9 (fly Rrp45) via CRISPR/Cas9. My preliminary studies show that distinct pathogenic variants within different or the same RNA exosome gene cause a spectrum of organismal phenotypes including reduced viability, behavioral defects, and defects in brain morphology compared to wildtype control flies. In addition, I have extended my analysis to survey the transcriptome of each disease-linked RNA exosome mutant fly compared to wildtype flies and have identified aberrant levels of key functionally important neuronal transcripts via bulk and single-nuclei transcriptomic approaches. Moreover, we have employed quantitative mRNA imaging technology throughout the entire *Drosophila* brain via Hybridization Chain Reaction (HCR) RNA-FISH to visualize defects in proper mRNA expression and localization. Furthermore, to examine RNA exosome complex/integrity, we utilized mass-spectrometry based approaches in brain-enriched tissue of RNA exosome mutant flies compared to wildtype controls. In sum, this study advances our understanding of RNA exosome-linked neurological

disease and provides insight into the distinct tissue-specific consequences caused by alterations in subunits within a single RNA processing complex.

**Disclosures:** **L. Higginson:** None. **M. Torstrick:** None. **N. Elias:** None. **J. Burford:** None. **D.J. Morton:** None.

**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.20/B54

**Topic:** A.07. Developmental Disorders

**Title:** Development and characterization of cell-based models of PTEN Hamartoma Tumor Syndrome

**Authors:** C. PAPADOPOULOS[1], J. RUDOLPH[1], K. MUELLER[1], P. FRIESS[1], C. TAN[2], A. SPASOVA[2], ***R. GROTH**[2], P. ELVIN[3];
[1]Evotec SE, Hamburg, Germany; [2]BridgeBio Pharma, Inc, Palo Alto, CA; [3]PTEN Res. Fndn., Gloucestershire, United Kingdom

**Abstract:** Germline mutations in the tumor suppressor gene PTEN result in a spectrum of multisystem disorders collectively referred to as PTEN hamartoma tumor syndrome (PHTS). Manifestations may include benign tumor-like growths (hamartomas), increased cancer risk, and neurological comorbidities such as macrocephaly, autism spectrum disorder, intellectual dysfunction, and in some cases, epilepsy. Here we developed murine and human neuronal cell-based models of PHTS to support drug discovery efforts. Adenoviral PTEN shRNA transduction of primary mouse hippocampal neurons on the first day in vitro (DIV) resulted in almost complete loss of PTEN protein expression by DIV10. By DIV14, knockdown of PTEN resulted in an increase in neurite outgrowth and branching, increased pAKT levels, and an increase in network burst duration as measured by multielectrode array (MEA). Similarly, knockdown of PTEN by ≥50% using an antisense oligonucleotide (ASO) approach in human iPSC-derived neurons led to increased pAKT levels and an increase in network burst duration. We utilized these models to screen tool compounds against PI3K pathway targets. Pan-PI3K pan inhibition or mTOR inhibition normalized pAKT levels and reversed the PTEN KD-induced hyperexcitability phenotype. Interestingly, whereas the PI3Kα inhibitor, alpelisib, restored pAKT levels, the PI3Kβ inhibitor, GSK2636771, had no effect. Given that dysregulation of PI3K signaling is a common feature of other disorders, including Fragile X syndrome and Rett syndrome, determining the mechanisms by which the PI3K pathway drives pathophysiology may inform treatment of diseases with overlapping manifestations. In sum, these cell-based models can be used to finely dissect signaling pathways underlying PTEN dysfunction in neurons to support the identification of candidate drugs to address the neurological manifestations of PHTS.

**Disclosures:** **C. Papadopoulos:** 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.; Evotec SE. **J. Rudolph:** 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.; Evotec SE. **K. Mueller:** 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.; Evotec SE. **P. Friess:** 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.; Evotec SE. **C. Tan:** A. Employment/Salary (full or part-time); BridgeBio Pharma, Inc. **A. Spasova:** A. Employment/Salary (full or part-time); BridgeBio Pharma, Inc. **R. Groth:** A. Employment/Salary (full or part-time); BridgeBio Pharma, Inc. **P. Elvin:** None.

**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.21/B55

**Topic:** A.07. Developmental Disorders

**Support:** NIH grant UG3 TR003897

**Title:** The unexpected and novel mitochondrial phenotype of the ex vivo patient-derived cellular model for SYNGAP1 encephalopathy

**Authors: M. UITTENBOGAARD**[1], A. GROPMAN[2], *A. CHIARAMELLO[1];
[1]Anat. and Cell Biol., George Washington Univ. Med. Ctr., Washington, DC;
[2]Neurodevelopmental Pediatrics and Neurogenetics, Children's Natl. Med. Ctr., Washington, DC

**Abstract:** A hallmark of brain metabolism is the dynamic coupling between energy demand and supply that involves a constant regulation of mitochondrial bioenergetics at prenatal and postnatal stages of brain development. The brain is highly dependent on mitochondrial homeostasis for ATP production via oxidative phosphorylation.
Our study focuses on the SYNGAP1 syndrome, an intractable neurodevelopmental disorder, with the long-term objective of designing novel therapeutic avenues. Its pathogenic mechanisms remain elusive due to its ultra-rare frequency of 1/10,000 and its relatively recent documentation as a neurodevelopmental disorder. The SYNGAP1 syndrome is caused by sporadic pathogenic nuclear variants mapping in the *SYNGAP1* gene, known to play an essential role in brain development and functions. The *SYNGAP1* gene encodes a brain-specific synaptic Ras GTP-ase activating protein essentially localized in dendritic spines of cortical pyramidal neurons. Patients with the SYNGAP1 syndrome exhibit neurodevelopmental delay, intellectual disability, epileptic

encephalopathy, and autism spectrum disorder.
The main question addressed in this study is whether the SynGAP1 syndrome could be in part due to a dysregulated mitochondrial energy metabolism. Our study focused on a 3-year-old male born with initial clinical manifestations of seizures, developmental motor and sensory delays accompanied by speech delay and social issues, all evocative of mitochondrial etiology. We undertook a comprehensive genetic analysis of the mitochondrial and nuclear genomes by long-range PCR followed by massively parallel sequencing (MitoNGS) and whole exome sequencing (WES), respectively. While the MitoNGS analysis did not reveal any mitochondrial pathogenic variants or large deletions, the WES analysis revealed the pathogenic heterozygous nuclear variant c.1783del (p.L595Cfs*55) in the *SYNGAP1* gene causing a frameshift variant located in exon 11 of 19.
To elucidate the SYNGAP1-mediated mitochondrial energy signature, we opted for patient-derived fibroblasts since the nuclear-mitochondrial genetic background alters metabolic efficiency. Using the Seahorse technology, we found a profound deficit in the spare energy capacity that is required for cells to sustain a high energy demand. Furthermore, the patient's fibroblasts displayed a defective mitochondrial metabolic plasticity preventing the use of glycolysis to curtail the energy deficit.
In conclusion, our study provides the first evidence of dysregulated mitochondrial energy metabolism associated with the SYNGAP1 syndrome in an *ex vivo* patient-derived cellular model.

**Disclosures:** **M. Uittenbogaard:** None. **A. Gropman:** None. **A. Chiaramello:** None.

**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.22/B56

**Topic:** A.07. Developmental Disorders

**Support:** Women in science grant L'oreal-Unesco-AMC 2022
IBRO Early Career Awards Program 2022

**Title:** Analysis of the impact of gestational diabetes on gene regulation and clinical aspects of neurodevelopment

**Authors: *M. E. ROJAS QUINTANA**[1], C. A. ZABALA BELLO[2], H. M. RIVERA ESCOBAR[3], K. M. LÓPEZ MARTÍNEZ[1], I. F. PINEDA SIERRA[4], A. K. PÉREZ VÁZQUEZ[5], T. GONZÁLEZ LÓPEZ[1], E. BAUTISTA RODRÍGUEZ[1];
[1]Univ. Popular Autónoma del Estado de Puebla, Puebla, Mexico; [2]Grupo de Investigación en Genética Animal, Univ. Nacional de Colombia, Bogotá, Colombia; [3]Dept. de Estudios Interdisciplinarios, Univ. de Tolima, Tolima, Colombia; [4]Hosp. de la Mujer, Puebla, Mexico; [5]Hosp. Infantil, Tlaxcala, Mexico

**Abstract:** Gestational diabetes (GD) is a global health problem with severe consequences at different levels in newborns. Few studies report the impact on neurodevelopment and its association with biological and clinical biomarkers. In this regard microRNAs (miRNAs) show excellent characteristics to be used as indicators of pathophysiological status. Therefore, the aim of this project was to perform a comparative analysis of miRNA expression and to relate them to aspects of neurodevelopment in order to understand the pathophysiology of the disease. The study consisted in the analysis of two groups of newborns, the first one exposed in-utero to GD and the second one was a control group. Neurodevelopmental assessment was performed using the EDI scale before 6 months of age and the extraction of mirNAs from Guthrie Cards, to later perform next generation sequencing by Illumina. The GD group showed a decrease in the Apgar index and gestational age as well as the presence of macrosomia and/or some metabolic alterations or malformations. Regarding the EDI index, the GD group showed decreased gross motor skills, language skills and increased biological risk factors. In the sequencing results, 29 differentially expressed miRNAs were found, interestingly all underexpressed within which mir 103a.1.5p, mir 103a.3p, mir 107, mir 122.3p, mir 187.5p, mir 1910.3p, mir 3135b, mir 3160.5p and mir 4268 stand out. Enrichment analysis showed relationship with pathways associated with cell division, gland development, chromatin modification, tube morphogenesis, response to hypoxia, brain development, embryonic stem cell differentiation and carbohydrate metabolism. These results will allow us to further understand the pathophysiology of the disease and identify new therapeutic targets or early diagnostic or prognostic biomarkers.

**Disclosures: M.E. Rojas Quintana:** None. **C.A. Zabala Bello:** None. **H.M. Rivera Escobar:** None. **K.M. López Martínez:** None. **I.F. Pineda Sierra:** None. **A.K. Pérez Vázquez:** None. **T. González López:** None. **E. Bautista Rodríguez:** None.

**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.23/B57

**Topic:** A.07. Developmental Disorders

**Support:** NIH NINDS 5K08NS112598-02

**Title:** Down-regulation and impaired activation of EGR1 in Tuberous Sclerosis Complex

**Authors: *K. WINDEN**, J. RUIZ, T. PHAM, N. TEANEY, M. SAHIN;
Boston Children's Hosp., Boston, MA

**Abstract:** Tuberous sclerosis complex (TSC) is a genetic disorder caused by heterozygous variants in either *TSC1* or *TSC2*, and it is associated with epilepsy, autism spectrum disorder (ASD), and intellectual disability. On a molecular level, loss of TSC1/2 leads to disinhibition of the mechanistic target of rapamycin complex 1 (mTORC1), a central kinase involved in growth and proliferation. Many neuronal abnormalities in TSC have been attributed to the increased

phosphorylation of known mTORC1 targets. However, several studies have identified transcriptional changes in TSC1/2-deficient neurons, but the mechanisms underlying these changes remain poorly understood. We found that the immediate early gene, EGR1, was down-regulated at the transcript and protein levels in cortical neurons in an animal model of TSC. In addition, we observed reduction of EGR1 and several of its transcriptional targets in TSC2-deficient human stem cell-derived neurons. To further understand the mechanism of decreased expression of EGR1 in TSC2-deficient neurons, we examined the activity dependence of the EGR1 promoter. Remarkably, we found that activation of the EGR1 promoter due to depolarization was significantly impaired in TSC2-deficient neurons. These data demonstrate that EGR1 is dysregulated due to loss of TSC in neurons and that this alteration may be associated with dysfunction within the signaling pathways activated by neuronal activity.

**Disclosures: K. Winden:** None. **J. Ruiz:** None. **T. Pham:** None. **N. Teaney:** None. **M. Sahin:** None.

**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.24/B58

**Topic:** A.07. Developmental Disorders

**Support:** Italian Ministry of Health.

**Title:** Maldi imaging mass spectrometry as a new tool for molecular histology in epilepsy surgery

**Authors: *R. GARBELLI**, D. DE SANTIS, M. DE CURTIS, C. CAGNOLI;
Epilepsy Unit, Inst. Neurologico Carlo Besta, Milan, Italy

**Abstract:** In selected patients with drug resistance focal seizures, epilepsy surgery is a safe and effective treatment. The spectrum of structural brain lesions histologically-detected is wide: Malformation of Cortical Development (MCD), particularly the different Focal Cortical Dysplasias (FCD), hippocampal sclerosis and low grade developmental tumor are highly represented both in children and adults. Histological diagnosis, currently based on microscopically visible alterations and on the level of expertise of pathologists, largely influence the post-surgical seizure outcome. For certain pathologies, the diagnosis based on microscopic hallmarks remains challenging and their incidence and clinical presentation show several discrepancies among centers. Thus, there is an urgent need to integrate the standard neuropathological workup with new and unconventional techniques. **M**atrix **a**ssisted **l**aser **d**esorption/**i**onization **i**maging **m**ass **s**pectrometry (MALDI IMS) is a powerful technique for label-free bioanalysis used to investigate, in a single tissue section, the spatial distribution of thousands of biomolecules which can be correlated with traditional histological evaluation. To optimize “standard operating protocol” for MALDI IMS analysis of peptides on formalin-fixed

paraffin embedded tissue sections (FFPE), we present preliminary experiments using tissue sections from patients with a histological diagnosis of type II FCD, a developmental cortical malformation frequent cause of drug-resistance epilepsy. Histology and immunohistochemistry were used for a meaningful interpretation of the MALDI IMS data. Unsupervised classification of the spectra, achieved by hierarchical clustering or by principal component analysis, is able to differentiate distinct histopathological features, such as gray matter and white matter boundaries, the core of the dysplastic lesion and the adjacent perilesional area, as validated on immunoreacted-adjacent sections. Moreover, we show a good correlation between peptide intensity map and immunohistochemistry of the correspondent protein. We also identify a list of peptides that discriminate the lesion core from the perilesional tissue. An optimized "standard operating protocol" for MALDI IMS on FFPE was developed to enhance spatial resolution and reproducibility. The identification of discriminant peak lists will be relevant in cases where diagnostic uncertainties and controversies persist or when small or fragmented biopsy samples are available. This will allow us to expand its applicability for different epileptogenic lesions more challenging in routine diagnostic practice.

**Disclosures:** **R. Garbelli:** None. **D. De santis:** None. **M. De Curtis:** None. **C. Cagnoli:** None.

**Poster**

**PSTR004. Molecular Mechanisms of Neurodevelopmental Disorders I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR004.25/Web Only

**Topic:** B.10. Demyelinating Disorders

**Support:** KAKENHI 19K08065
KAKENHI 22K07611

**Title:** Localization Mechanism of Myosin Id, an ASD Risk Gene Product in Dendritic Spines.

**Authors: *T. SASAKI**, Y. TAKEI;
Univ. of Tsukuba, Tsukuba, Japan

**Abstract:** Dendritic spines, the postsynaptic compartments atexcitatory synapses, are capable of changing their shape and size to modulatesynaptic transmission. The actin cytoskeleton and a variety of actin-bindingproteins play a critical role in the dynamics of dendritic spines.Abnormalities of spine dynamics are implicated in several psychiatricdisorders, such as schizophrenia and Autism Spectrum Disorder (ASD). Class Imyosins are monomeric motor proteins that move along actin filaments using theenergy of ATP hydrolysis. Of these class I myosins, myosin Id has been reportedto be expressed in neurons, whereas its subcellular localization in neuronsremained unknown. The linkage analysis suggests that myosin Id is a potentialrisk gene for ASD implied that myosin Id might play an important role indendritic spines. Here, we investigated the subcellular localization of myosinId and determined the domain responsible for it. We found that myosin Id isenriched in the dendritic spines of primary

hippocampal neurons. The mutantform lacking the TH1 domain is less distributed in dendritic spines than is thefull-length form.Taken together, our findings reveal that myosin Idlocalizes in dendritic spines through the TH1 domain. Our results showing thatmyosin Id is enriched in dendritic spines raise the possibility that myosin Idregulates synaptic transmission in dendritic spines and, furthermore, that itsdysfunction would result in ASD. These results provide the first clues tounderstand the role of this molecule in the development and pathophysiology ofASD.

**Disclosures:** **T. Sasaki:** None. **Y. Takei:** None.

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.01/B59

**Topic:** B.04. Synaptic Transmission

**Support:** Australian Research Council

**Title:** An exciting new tool for neuroscience: reverse engineering viral induced synaptogenesis

**Authors: *S. KEATING**[1], J. BINGHAM[1], K. ARDIPRADJA[1], J. BROADBENT[2], U. BOSE[2], V. SUNDARAMOORTHY[1];
[1]CSIRO, Geelong, Australia; [2]Univ. of Queensland, Brisbane, Australia

**Abstract:** Advancement in neuroscience research has unravelled many key aspects about the dynamics and formation of synapses which are the communication ports between neurons. However, there is still more to learn about the molecular mechanisms that initiate and control filopodia formation and establishment of synaptic contacts. In this project, we propose to utilise the unique trans-synaptic transfer ability of rabies virus as an innovative tool to investigate synaptogenesis.
The glycoprotein of rabies virus is known to be essential for the specific trans-synaptic transmission of rabies virus. In our study, we identified that glycoprotein derived from a highly-neuroinvasive rabies strain has an ability to drastically increase filopodia and synapse formation in cultured neurons. This increased synapse formation enabled efficient transfer of the virus particles. We hypothesised that the investigating this novel ability of rabies glycoprotein to increase filopodia and synapse formation will reveal new information about synaptogenesis. Using proximity labelling based interactome analyses, this project has successfully identified a range of synaptic proteins that interact directly with the rabies glycoprotein to increase filopodia and synapse formation. These are now being further characterised through proteomic assays, western blot analyses and ELISAs with hopes of unravelling their specific role in synapse formation. This could lead to the identification of new signalling mechanisms controlling synapse formation. Advanced imaging techniques such as confocal and super-resolution microscopy are also being employed to examine the precise localisation and role of rabies glycoprotein and its interacting proteins in influencing synapse formation. This comprehensive

approach aims to expand our understanding of the complex processes governing synapse development and provide valuable knowledge about the intricate neural networks that comprise the brain.

**Disclosures:** **S. Keating:** None. **J. Bingham:** None. **K. Ardipradja:** None. **J. Broadbent:** None. **U. Bose:** None. **V. Sundaramoorthy:** None.

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.02/B60

**Topic:** B.04. Synaptic Transmission

**Support:** NIH Grant NS096092

**Title:** Modulation of optogenetically-evoked IPSCs by μ-opioid receptors in subtypes of subicular pyramidal cells

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

**Abstract:** The subiculum serves as the major output of the hippocampal formation, and it's involved in a variety of complex physiological functions. However, in pathological conditions, its local excitatory circuits are able to generate hypersynchronous discharges that may propagate to distant cortical regions. Despite numerous studies providing evidence of two distinct populations of subicular pyramidal neurons (intrinsically bursting and regular firing IB, RF, respectively), the diversity of the presynaptic inhibitory inputs remains unknown. Yet, this is crucial for understanding how specific populations of GABAergic cells physiologically regulate functionally distinct pyramidal neurons. Moreover, since parvalbumin-expressing interneurons (PVs) have been implicated in the generation of epileptiform activity, exploring differences in their terminals may uncover new aspects of circuit regulation. Here, we investigated the role of μ-opioid receptor (MOR) expression in PV terminals targeting IB and RF subicular pyramidal neurons. To classify cells, their excitability and firing patterns were initially evaluated using potassium-based intracellular solutions. Then, the same neurons were re-patched with pipettes containing cesium and QX314 and held in voltage-clamp at +10 mV to record outward inhibitory postsynaptic currents (IPSCs), which were triggered by brief blue light pulses (0.5 ms) in slices prepared from PV-channelrhodopsin mice. IPSCs were recorded at 0.1 Hz and, after a baseline of 3 minutes, the μ-opioid receptor agonist DAMGO (5μM) was applied for 12 minutes. We found a similar steady-state reduction (~45%) of IPSC amplitude in IB (n=17) and RF(n=19), but different kinetics. In both cases, the effect of DAMGO was blocked by the opioid receptor antagonist naloxone (10μM, n=6 IB and n=6 RF). The kinetic difference in the effect of DAMGO on the IPSC recorded in IB vs RF was abolished in the presence of the metabotropic glutamate receptor antagonist MCPG (500μM, n=5 IB and n=6 RF). We are currently testing the

hypothesis that DAMGO activation of glial MORs triggers a transient glutamate release specifically acting on metabotropic receptors selectively expressed by IB cells.

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

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.03/B61

**Topic:** B.04. Synaptic Transmission

**Support:** NIH Grant F31NS122424
NIH Grant R01NS078179

**Title:** Distinct neuronal subtypes use intersecting molecular and organizational diversity to generate synaptic heterogeneity

**Authors: *A. T. MEDEIROS**[1], S. J. GRATZ[1], A. DELGADO[1], J. T. RITT[2], K. M. O'CONNOR-GILES[1];
[1]Neurosci., [2]Carney Inst. for Brain Sci., Brown Univ., Providence, RI

**Abstract:** Communication in the nervous system relies on neurotransmitter release at synapses with heterogeneous properties. Neurotransmitter release is triggered by $Ca^{2+}$ influx through voltage-gated $Ca^{2+}$ channels (VGCCs) localized at active zones. How or if VGCC levels determine probability of release ($P_r$) has been debated recently, so we investigated how channel levels correlate with $P_r$ at distinct excitatory synaptic subtypes. We take advantage of two glutamatergic neuronal subtypes at the Drosophila neuromuscular junction, type Ib and Is. Type Is active zones have higher action-potential induced $Ca^{2+}$ influx and a higher $P_r$ than type Ib, providing a model to study VGCC organization at two closely related synapses with distinct release properties. We have endogenously tagged the sole Drosophila Cav2 channel and, using functional imaging, found that VGCC levels are highly predictive of $P_r$ at individual active zones within both type Is and type Ib subtypes. However, when comparing between these neuronal subtypes, VGCC levels no longer predict $P_r$. To explain this paradox, we used STORM single molecule localization microscopy and found underlying differences in VGCC density, but not number, between subtypes, suggesting that organizational differences in VGCC contribute to their distinct release properties. We next investigated the composition of VGCC auxiliary subunits, which influence both channel trafficking and function, at each synaptic subtype. To determine auxiliary subunit molecular composition at type Ib and Is synapses, we endogenously tagged the sole Drosophila β subunit Ca-β and the two α2δ subunits, Straightjacket and Stolid, shown to function in motor neurons. All three subunits are expressed in the larval brain, albeit with different expression patterns. However, only Ca-β and Straightjacket are observed at the neuromuscular junction. Ca-β is expressed at similar levels between type Ib and Is synapses. In contrast, Straightjacket is expressed at lower levels at the high-$P_r$ type Is active zones. Similarly,

active zone cytomatrix protein Bruchpilot/CAST levels are lower at type Is synapses. Together, our findings reveal a context-specific role for VGCC levels in determining release probability.

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

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.04/B62

**Topic:** B.04. Synaptic Transmission

**Support:** STI2030-Major Projects-2022ZD0205900
nsfc 32200784

**Title:** Distinct dynamic state in synaptic vesicle release captured by time resolved cryo-electron tomography

**Authors: *C. TAO**;
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**Abstract:** Distinct dynamic state in synaptic vesicle release captured by time resolved cryo-electron tomography
Changlu Tao[1,2]*, Chongli Tian[1,2]*, Yuntao Liu[1,3]*, Zhenhang Lu[1,2], Lei Qi[1], Dongqing Shi[1], Xiaowei Li[1], Leiqing Yang[2], Zhenhang Liao[2], Pak-Ming Lau[1,2], Z. Hong Zhou[3], Guo-Qiang Bi[1,2]
[1]University of Science and Technology of China; [2]Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences; [3]University of California, Los Angeles
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Synaptic vesicle (SV) release is the predominant mode of neural transmission and depends on precisely regulated SV exocytosis. Here, we have established a pipeline of imaging intact cultured hippocampal neurons with cryo-electron tomography that enables visualization of intact synapses at molecular resolution. Our data shows there are three distinct types of SVs interacting with the presynaptic membrane: ‘tethered’, ‘contacting’, and ‘omega-shaped’ SVs. A “flash-freeze” scheme of sample preparation with time-resolved optogenetic stimulation allows for capturing snapshots of synaptic dynamics and revealing the distinct types of SVs are the intermediate states of SV exocytosis. Our data shows that synaptic vesicle exocytosis undergoes two phases: a fast phase as the vesicle fused with a narrow pore for transmitter release accompanied by rapid vesicle shrinkage; then these vesicles can detach from or fuse completely with the presynaptic membrane, corresponding to the ‘kiss-and-run’ and ‘full collapse’ processes, respectively. One action potential can trigger a bulk of vesicle release, and ‘kiss-and-run’ is the predominant mode of vesicle recycling. In summary, we provide a picture of the dynamic process of vesicle release in the native synapse at high spatiotemporal resolution.
**Keywords:** Synaptic transmission, Vesicle exocytosis, Cryo-electron tomography

**Disclosures: C. Tao:** None.

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.05/B63

**Topic:** B.04. Synaptic Transmission

**Support:** JSPS KAKENHI, Grant Number JP22H02721
JSPS KAKENHI, Grant Number JP22K19360
JST SPRING, Grant Number JPMJSP2110

**Title:** Dual actions of cAMP on action potential and transmitter release in an axon of a cerebellar Purkinje cell

**Authors: *K. FURUKAWA**, S.-Y. KAWAGUCHI;
Dept. of Biophysics, Grad. Sch. of Science, Kyoto Univ., Sakyo-ku, Kyoto-shi, Japan

**Abstract:** In the central nervous system, most synapses exhibit potentiation of neurotransmitter release by cAMP, although the underlying presynaptic mechanism still remains elusive. Here, taking advantages of direct axonal bouton recordings, we examined how cAMP controls synaptic outputs from a Purkinje cell (PC), an inhibitory cerebellar neuron. By an adeno-associated virus (AAV) vector, we fluorescently labelled cultured PCs. First, simultaneous somatic patch-clamp recordings were performed from a PC and its target neuron. Increase in intracellular cAMP by forskolin, a cell membrane-permeable adenylyl cyclase activator, unexpectedly, weakened the evoked IPSC in amplitudes. Additionally, the synaptic delay was increased after the forskolin application in a manner dependent on the axon length, suggesting a novel action of cAMP on a PC in clear contrast to previous studies on other neurons. To examine the underlying mechanism, we performed dual recordings from a PC soma and its axon. Forskolin slowed the axonal action potential (AP) propagation and attenuated the AP amplitude, suggesting that cAMP slows and attenuates the AP conduction in PC axons. By a direct patch-clamp recording from a PC axon, we also found that the axonal currents through voltage-gated $Na^+$ channels were decreased by forskolin. Next, we performed dual recordings from a PC axon terminal and its target neuron. Voltage command with an AP waveform was applied to the voltage-clamped terminal, and the resultant presynaptic $Ca^{2+}$ influx and evoked IPSCs were recorded. Weakened AP waveforms, mimicking attenuation of AP by forskolin, showed a decrease in the $Ca^{2+}$ currents and IPSCs, suggesting that the AP-attenuation by cAMP was responsible for the diminished presynaptic $Ca^{2+}$ influx and subsequent smaller synaptic vesicular release. Furthermore, we attempted to clarify the effect of cAMP on release machinery independently from the AP conduction, and quantitatively measured the $Ca^{2+}$ influx, $Ca^{2+}$ sensitivity of release, and size of readily releasable pool (RRP) of synaptic vesicles. Taken all these results together, our data indicate that cAMP modulates both the axonal AP conduction and presynaptic neurotransmitter release, dynamically controlling the timing and efficacy of synaptic outputs from PCs.

**Disclosures:** **K. Furukawa:** None. **S. Kawaguchi:** None.

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.06/C1

**Topic:** B.04. Synaptic Transmission

**Title:** Molecular mechanism of synaptic vesicle depriming dynamics prior to fusion

**Authors:** ***C. LEE**[1], S. OUD[1], N. BROSE[2], J. RHEE[1];
[1]Group of Synapse Physiology, Dept. of Mol. Neurobio., [2]Dept. of Mol. Neurobio., Max Planck Inst. For Multidisciplinary Sci., Göttingen, Germany

**Abstract:** The significance of synaptic vesicle (SV) priming for accurate neural information transferring has been well-established. However, the specific molecular model for dynamic identity of SV derpiming that revert trans-SNARE complex assembly, has yet to be identified. As a result of using N-ethylmaleimide (NEM), which inhibits NSF activity, and genetical mutant mice lacking the presynaptic proteins involved in SV priming and fusion, we found that the SV depriming doubled down on vesicular release probability and inhibited the rate of short-term depression. In particular, SV depriming only occurred after Munc13 priming activity and furthermore, the C1 domain in Munc13-1 was an absolutely required the dynamic regulation of the priming-depriming activity equilibrium prior to SV fusion. We speculated that the SV depriming activity may allow primed SVs to remain in a fairly heterogeneous dynamic state rather than in a stable waiting-for-fusion state, allowing synaptic plasticity through stable and sustained changes in synaptic transmission.

**Disclosures:** **C. Lee:** None. **S. Oud:** None. **N. Brose:** None. **J. Rhee:** None.

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.07/C2

**Topic:** B.04. Synaptic Transmission

**Support:** AMED under Grant Number JP21gm1310012

**Title:** Function of Hs3st4 in subplate neuron in deveropmental cortex

**Authors: *A. MORIOKA**, C. MARUYAMA;
Tokyo Metropolitan Inst., Setagaya-ku / TOKYO, Japan

**Abstract:** In mammals, the cerebral cortex consists of six layers. Neural migration must be regulated appropriately to form layered cortical structures at the embryonic stage. In the developing neocortex, excitatory neurons born at the ventricular zone migrate toward the pial surface using two different migration modes, multipolar migration and locomotion. We have previously reported that subplate neurons (SpNs) facilitate the conversion of migratory modes through synaptic transmission (Chiaki Ohtaka-Maruyama et al, science 2018). However, the molecular mechanisms regulating the synaptic transmission are unknown. Subplate (SP) layers are rich in proteoglycans, such as HSPGs and CSPGs, and extracellular matrix, such as fibronectin and collagen. Furthermore, we have previously found that Hs3st4 (heparan sulfate-3*O* -sulfotransferase 4), which modifies the sulfate group to the heparan sulfate chains, is highly expressed in the SP layer. But their physiological significance is unknown. In this study, we analyzed the function of Hs3st4 in SpNs. SpNs are known to regulate neuronal migration via synaptic transmission and the formation of the thalamocortical neural circuit. We hypothesized that Hs3st4 might be involved in these functions. We then investigated which heparan sulfate proteoglycans are expressed explicitly in SpNs using RNA Scope in situ hybridization. Neurexin 1 (synapse organizer) is highly expressed in the SpNs and co-expressed with Hs3st4. We also screened postsynaptic proteins expressed in migrating neurons using microarray data of migrating neurons and found that Neuroligin2, known as a Neurexin-specific ligand, is expressed in those neurons. These results suggest that Neurexin1 and Neuroligin 2 might be involved in the transient synaptic transmission between SpNs and migrating neurons. Also, there is a possibility that Hs3st4 regulates the function of Neurexin 1 by adding a sulfate group at the SP layer. While, Hs3st4 was also expressed in axons, projecting from subplate neurons to cortical layer IV at the postnatal stage. Hs3st4 may also be associated with the projection of the thalamocortical axon to the cortical IV layer. These results raised the possibility that Hs3st4 regulates synaptic transmission and thalamocortical projections by modifying the sulfate group to Neurexin 1 in the SP layer.

**Disclosures: A. Morioka:** None. **C. Maruyama:** None.

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.08/C3

**Topic:** B.04. Synaptic Transmission

**Support:** NIH Grant DC014093

**Title:** Deciphering CAST/ELKS regulation in presynaptic calcium channel targeting.

**Authors: *M. BENDALE**[1,2,3], H. LI[2], S. M. YOUNG, Jr[2,4];
[2]Dept. of Anat. and Cell Biol., [3]Cell and Developmental Biol. Grad. Program, [4]Dept. of Otolaryngology, Iowa Neurosci. Inst., [1]Univ. of Iowa, Iowa City, IA

**Abstract:** The diversity of information encoding by neuronal circuits is regulated by the magnitude and location of $Ca^{2+}$ entry though voltage-gated $Ca^{2+}$ channels ($Ca_V$). In the mammalian central nervous system (CNS), $Ca_V2.1$ is the critical subtype for CNS function, since it is the most efficient $Ca_V2$ subtype triggering action potential (AP) -mediated synaptic vesicle (SV) release. The AZ comprises of a dense network of proteins that regulate synaptic function. CAST/ELKS are highly conserved large multidomain core active zone proteins that regulate presynaptic $Ca_V2$ channel levels and synaptic transmission. However, the molecular mechanisms by which CAST/ELKS regulate presynaptic calcium channel targeting are unknown. To identify specific domains in CAST/ELKS which regulate presynaptic calcium channel targeting, we expressed mutant CAST/ELKS protein which deleted known binding sites to other active zone proteins at CAST/ELKS null presynaptic calyx of Held terminals. Direct presynaptic $Ca^{2+}$ current recordings were made using whole cell patch clamp electrophysiology to measure the impact of the mutant CAST/ELKS proteins on presynaptic calcium current levels. Based on our work, we have identified binding sites for CAST/ELKS that regulate presynaptic $Ca_V2$ levels. These results and their impact on synaptic transmission will be discussed.

**Disclosures: M. Bendale:** None. **H. Li:** None. **S.M. Young:** None.

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.09/C4

**Topic:** B.04. Synaptic Transmission

**Support:** Wellcome Trust - Technology Development Grant 221295

**Title:** SV2A is expressed in subpopulations of glutamatergic and GABAergic synapses: implications for PET brain imaging

**Authors: *T. WONG**[1], Z. QIU[1], C. WIMBERLEY[1], C. ALCAIDE-CORRAL[2], T. E. F. MORGAN[2], H. MCERLAIN[3], A. SUTHERLAND[3], A. TAVARES[2], S. G. N. GRANT[1];
[1]Ctr. for Clin. Brain Sci., [2]Ctr. for Cardiovasc. Sci. and Edinburgh Imaging, Univ. of Edinburgh, Edinburgh, United Kingdom; [3]Sch. of Chem., Univ. of Glasgow, Glasgow, United Kingdom

**Abstract:** Loss or damage of synapses underlies a wide variety of brain disorders and there is a pressing need to monitor synapse pathology in living individuals. Positron emission tomography (PET) radiotracers that target synaptic vesicle protein 2A (SV2A) have shown promise in animal and human studies. SV2A tracers have been reported to target all synapses and PET measurements are used as a correlate of the synapse density in brain regions. Here, we ask whether SV2A is found in all synapses and if the PET tracer signal correlates with the density of

SV2A-positive synapses. Using fluorescent immunolabelling and confocal spinning disk microscopy at single-synapse resolution, we compared the expression of SV2A with a panel of presynaptic and postsynaptic protein markers targeted to glutamatergic and GABAergic terminals in mouse (N=3) and human (N=3) brain tissue. Only 65% of presynaptic terminals and, interestingly, 40% of postsynaptic terminals were colocalised with SV2A expression in mouse cortex, hippocampus, thalamus and striatum. In human cortex, only 23% of inhibitory synapses and 30% of excitatory synapses express SV2A. Furthermore, SV2A-labelled synaptic terminals showed a wide range of sizes and intensity indicating that SV2A PET tracer signals will be affected by the populations of these synapses. Our findings show that, in both mouse and human brain, SV2A is present in subsets of excitatory and inhibitory synapses. Crucially, this indicates that SV2A is unlikely to be a reliable correlate of synapse density in all brain regions and, consequently, that PET imaging data utilising SV2A tracers may not capture all synapse pathology. Further studies are required to fully understand how we should interpret such PET studies in monitoring human diseases, including whether SV2A synapses are among those subtypes differentially vulnerable or resilient in each disease, and testing whether brain regional PET signal can be matched to SV2A subtype distributions. This will help identify patient populations that would benefit most from SV2A PET imaging.

**Disclosures:** **T. Wong:** None. **Z. Qiu:** None. **C. Wimberley:** None. **C. Alcaide-Corral:** None. **T.E.F. Morgan:** None. **H. Mcerlain:** None. **A. Sutherland:** None. **A. Tavares:** None. **S.G.N. Grant:** None.

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.10/C5

**Topic:** B.04. Synaptic Transmission

**Support:** EKFS_#2019_A94
Deutsche Forschungsgemeinschaft (DFG; FOR 1332, CRC/TRR 167)

**Title:** The amyloid precursor protein regulates synaptic transmission at medial perforant path synapses

**Authors: *M. LENZ**[1,2], A. EICHLER[2], P. KRUSE[2], C. GALANIS[2], D. KLEIDONAS[2,3,4], G. ANDRIEUX[5], M. BOERRIES[5,6], P. JEDLICKA[7,8,9], U. C. MULLER[10], T. DELLER[8], A. VLACHOS[2,11,12];
[1]Inst. of Neuroanatomy and Cell Biol., Hannover, Germany; [2]Dept. of Neuroanatomy, Inst. of Anat. and Cell Biology, Fac. of Medicine, Univ. of Freiburg, Freiburg, Germany; [3]Spemann Grad. Sch. of Biol. and Medicine, Univ. of Freiburg, Freiburg, Germany; [4]Fac. of Biology, Univ. of Freiburg, Freiburg, Germany; [5]Inst. of Med. Bioinformatics and Systems Medicine, Med. Ctr. - Univ. of Freiburg, Fac. of Medicine, Univ. of Freiburg, Freiburg, Germany; [6]German Cancer Consortium (DKTK), Partner Site Freiburg and German Cancer Res. Ctr. (DKFZ), Heidelberg,

Germany; [7]ICAR3R - Interdisciplinary Ctr. for 3Rs in Animal Research, Fac. of Medicine, Justus-Liebig-University, Giessen, Germany; [8]Inst. of Clin. Neuroanatomy, Neurosci. Center, Goethe-University Frankfurt, Frankfurt am Main, Germany; [9]Frankfurt Inst. for Advanced Studies, Frankfurt am Main, Germany; [10]Ruprecht-Karls Univ. Heidelberg, Inst. of Pharm. and Mol. Biotechnology, Bioinformatics and Functional Genomics, Heidelberg, Germany; [11]Ctr. for Basics in Neuromodulation, Fac. of Medicine, Univ. of Freiburg, Freiburg, Germany; [12]Ctr. BrainLinks-BrainTools, Univ. of Freiburg, Freiburg, Germany

**Abstract:** The perforant path provides excitatory input to the hippocampus. Due to its role in information processing and coding, entorhinal projections to the dentate gyrus have been studied in considerable detail. Nevertheless, synaptic transmission between individual connected pairs of entorhinal stellate cells and dentate granule cells remains to be characterized. In this study, we used mouse organotypic entorhino-hippocampal tissue cultures of either sex, in which the entorhino-dentate (EC-GC) projection is present and EC-GC pairs can be studied using whole-cell patch clamp recordings. The properties of EC-GC synapses formed by the lateral and medial entorhinal cortex were compared in wildtype cultures and differences in short-term plasticity were identified. Since the perforant path is severely affected in Alzheimer´s disease, we used tissue cultures of amyloid-precursor protein (APP)-deficient mice to examine the role of APP at this synapse. APP deficiency altered excitatory neurotransmission at medial perforant path synapses, which was accompanied by transcriptomic and ultrastructural changes. Moreover, presynaptic but not postsynaptic APP deletion in conditional APPflox/flox tissue cultures increased the excitatory transmission efficacy at perforant path synapses. In summary, these data suggest a physiological role for presynaptic APP at medial perforant path synapses that may be adversely affected under altered APP processing conditions.

**Disclosures: M. Lenz:** None. **A. Eichler:** None. **P. Kruse:** None. **C. Galanis:** None. **D. Kleidonas:** None. **G. Andrieux:** None. **M. Boerries:** None. **P. Jedlicka:** None. **U.C. Muller:** None. **T. Deller:** A. Employment/Salary (full or part-time); Thomas Deller has received an honorarium from Novartis for a lecture on human brain anatomy. **A. Vlachos:** None.

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.11/C6

**Topic:** B.04. Synaptic Transmission

**Title:** Exploring the molecular consequences of Abl kinase activity: insights into spontaneous synaptic transmission and synapse maintenance

**Authors: *M. KABIROVA**[1,2], I. MICHAELEVSKI[3];
[1]Univ. of Chicago, Chicago, IL; [3]Integrative Brain Sci. Ctr. - Ariel, Mol. Biol., [2]Ariel Univ., Ariel, Israel

**Abstract:** The Abl kinase family, comprising two members, Abl1 and Abl2, exhibits tissue-specific and context-dependent behaviors. In response to various extra- and intracellular signals, Abl can initiate processes such as DNA repair, cell death, cell differentiation, proliferation, migration, or retraction. The role of Abl kinase in the central nervous system (CNS) involves neurulation, axon guidance, and synaptic transmission. Our previous research demonstrated that Abl1 influences presynaptic release, while Abl2 regulates postsynaptic responses. We discovered that Abl2 activity affects the current density in excitatory synapses through the AMPA and NMDA receptors, while the downstream effects of Abl1 on the presynapse remain unknown. To address this question, we examined changes in the phosphorylation levels of synaptic proteins using mass-spectrometry. In three independent sets of biological replicates, we detected and quantified 3812 phosphorylation sites belonging to 1161 unique proteins. Our phosphoproteomic analysis provided a comprehensive understanding of the molecular consequences of Abl kinase activity. Activation or inhibition of Abl kinase led to significant alterations in phosphorylation patterns in hippocampal neurons, indicating the involvement of numerous protein kinases. Notably, kinases such as Src, PKA, PKC, ERK1/2, CDK5, casein kinase 2, and GSK3, which have known roles in regulating synaptic activity, plasticity, and development, were prominently affected. Bioinformatic analysis further supported the potential contribution of Abl kinase activity to synaptic transmission and maintenance. Among the 65 synaptic phosphoproteins showing enrichment, several were implicated in active zone composition (e.g., Bassoon, RIM, Piccolo) and docking, priming, and fusion processes (e.g., munc18, munc13, syntaxin 1, synaptotagmin, complexin). Complexin 2 and synaptotagmin 2 exhibited the strongest correlation with Abl kinase activity. Synaptotagmins and complexins exert opposing effects on both spontaneous and evoked release events. Previous studies have demonstrated that phosphorylation of presynaptic proteins, including complexins and synaptotagmins, profoundly influences neurotransmission in both stimulated and spontaneous contexts. Complexins play a crucial role in presynaptic maturation and synapse development related to spontaneous release. Additionally, our data align with previous findings indicating that Abl activation induces phosphorylation of NCAM1, eIF3a, and dephosphorylation of eIF4B, which are associated with neuronal activity, synapse development, and pruning.

**Disclosures: M. Kabirova:** None. **I. Michaelevski:** None.

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.12/C7

**Topic:** B.04. Synaptic Transmission

**Title:** Investigating the Synaptic Effects of CASK deficiency in Human Neurons

**Authors: *Y. NG**[1,2], J. A. JANAS[2], Z. LIU[2,3], J. S. POLEPALLI[1], T. SÜDHOF[2,3];
[1]Dept. of Anat., Natl. Univ. of Singapore, Singapore, Singapore; [2]Inst. for Stem Cell Biol. and

Regenerative Med., Stanford, CA; [3]Dept. of Mol. and Cell. Physiol., Howard Hughes Med. Inst., Stanford, CA

**Abstract:** Calcium/Calmodulin-dependent serine kinase (CASK) is a member of the MAGUK family of proteins and is located on the X chromosome. CASK deficiency results in microcephaly with pontine and cerebellar hypoplasia (MICPCH). CASK was first identified as an interactor with Neurexin-1 and studies have shown it to be a Mg2+-independent protein kinase that phosphorylates itself and Neurexin-1 via its PDZ domain. However, the role of CASK in organizing synapses is still unclear. To study CASK deficiency in human neurons, we used the CRISPR/Cas9 system to selectively target the first coding exon, yielding CASK knockout human ES cell lines. Using a previously published system of overexpressing the transcription factor Ngn2, we generated large number of human induced neurons (iN cells) for subsequent studies. We examined the expression levels of a panel of synaptic proteins to examine the synaptic effect of CASK deficiency. In addition, we examined the change in network activity in the CASK-deficient neuronal cultures and observed decreased network activity in CASK KO neurons. Future work will further examine the roles of various domains in CASK in order to elucidate the role of CASK in organizing synapses.

**Disclosures: Y. Ng:** None. **J.A. Janas:** None. **Z. Liu:** None. **J.S. Polepalli:** None. **T. Südhof:** None.

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.13/C8

**Topic:** B.04. Synaptic Transmission

**Support:** NIH Grant NS113955
NIH Grant NS112788

**Title:** $Ca^{2+}$-regulated expression of high affinity methylaminoisobutryic acid transport in hippocampal neurons inhibited by riluzole and novel neuroprotective aminothiazoles

**Authors: *J. D. ERICKSON**[1], H. WULFF[2];
[1]Neurosci. Ctr., LSU Hlth. Sci. Ctr., New Orleans, LA; [2]Pharmacol., Univ. of California Davis, Davis, CA

**Abstract:** High-affinity methylaminoisobutyric acid(MeAIB)/glutamine(Gln) transport activity regulated by neuronal firing occurs at the plasma membrane in mature rat hippocampal neuron-enriched cultures. Spontaneous $Ca^{2+}$-regulated transport activity was similarly inhibited by riluzole and by novel naphthalenyl substituted aminothiazole derivatives such as SKA-378. Here, we report that spontaneous activity is stimulated by 4-aminopyridine (4-AP) and that phorbol-myristate acetate (PMA) increases high $K^+$ stimulated transport activity that is inhibited by staurosporin. 4-AP-stimulated spontaneous and PMA-stimulated high $K^+$-induced transport is not

present at 7 days *in vitro* (DIV) and is maximal by DIV~21. The relative affinity for MeAIB is similar for spontaneous and high $K^+$-stimulated transport ($K_m$~50υM) suggesting that a single transporter is involved. While riluzole and SKA-378 inhibit spontaneous transport with equal potency ($IC_{50}$~1υM), they exhibit decreased (~3-5X) potency for 4-AP-stimulated spontaneous transport. Interestingly, high $K^+$-stimulated MeAIB transport displays lower and differential sensitivity to the two compounds. SKA-378-related halogenated derivatives of SKA-75 (SKA-219, SKA-377 and SKA-375) preferentially inhibit high $K^+$-induced expression of MeAIB transport activity at the plasma membrane ($IC_{50}$<25υM), compared to SKA-75 and riluzole ($IC_{50}$>100υM). $Ca^{2+}$-dependent spontaneous and high $K^+$-stimulated MeAIB transport activity is blocked by ω-conotoxin MVIIC, ω-agatoxin IVA, ω-agotoxin TK ($IC_{50}$~500nM) or cadmium ($IC_{50}$~20υM) demonstrating that P/Q-type $Ca_V$ channels that are required for activity-regulated presynaptic vesicular glutamate (Glu) release are also required for high-affinity MeAIB transport expression at the plasma membrane. We suggest that neural activity driven and $Ca^{2+}$ dependent trafficking of the high affinity MeAIB transporter to the plasma membrane is a unique target to understand mechanisms of Glu/Gln recycling in synapses and acute neuroprotection against excitotoxic presynaptic Glu induced neural injury.

**Disclosures:** **J.D. Erickson:** None. **H. Wulff:** None.

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.14/C9

**Topic:** B.04. Synaptic Transmission

**Title:** Structural and biochemical characterization of Gbeta-gamma interactions with a pre-fusion trans-SNARE mimetic

**Authors: *A. R. EITEL**[1], H. E. HAMM[2];
[1]Biochem., Vanderbilt Univ., Nashville, TN; [2]Dept. of Pharmacol., Vanderbilt Univ. Sch. of Med., Nashville, TN

**Abstract:** G-protein βγ heterodimers (Gβγ) liberated upon activation of presynaptic inhibitory G-protein Coupled Receptors ($G_{i/o}$ GPCRs) prevent neurotransmission downstream of $Ca^{2+}$ influx through direct interactions with the ternary N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex. The ternary SNARE complex is composed of synaptosomal-associated protein, 25kDa (SNAP-25), syntaxin-1A, and synaptobrevin-2. Previous work from the Hamm lab has shown that the primary site of Gβγ-SNARE interactions involve the C-terminus of SNAP-25 and the N-termini of $Gβ_1γ_2$. Therefore, our hypothesis is that Gβγ competes with the $Ca^{2+}$-sensor synaptotagmin for binding to the C-terminus of SNAP-25 in order to inhibit fusion. However, the precise mechanism underlying Gβγ-mediated inhibition remains unclear due to the lack of high-resolution structural data available for the Gβγ-SNARE complex. To address this, we have expressed and purified a pre-fusion ternary SNARE mimetic containing

a C-terminal truncation of synaptobrevin-2 which prevents full zippering of the SNARE complex. This partially zippered SNARE construct has a higher affinity for $G\beta_1\gamma_2$ than the fully zippered version as determined by microscale thermophoresis (MST). We stabilized the $G\beta_1\gamma_2$-SNARE interaction using a crosslinker and purified the complex via gel filtration chromatography. Peak fractions were analyzed using negative stain and cryo-electron microscopy. Our current low-resolution initial model suggests that $G\beta_1\gamma_2$ interacts with ternary SNARE only through the C-terminus of SNAP25. The region of $G\beta_1\gamma_2$ involved in Gα subunit interactions does not appear to overlap with the binding site for SNAP-25. We are currently collecting and processing additional cryo-EM data to provide an atomic resolution structure.

**Disclosures:** **A.R. Eitel:** None. **H.E. Hamm:** None.

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.15/C10

**Topic:** B.04. Synaptic Transmission

**Support:** MOST Grant 109-2311-B-002-008-MY3
NTU Grant NTU-CC-112L895404

**Title:** Pathogenic human a-Synuclein regulates fusion pore kinetics during catecholamine release

**Authors: *P.-C. CHEN**, C.-T. WANG;
Inst. of Mol. and Cell. Biol., Natl. Taiwan Univ., Taipei, Taiwan

**Abstract:** Parkinson's disease (PD) is the second most common neurodegenerative disease due to the massive death of dopamine neurons in the substantia nigra. In the past several decades, postmortem studies demonstrated that polyploidy or mutation of human αSynuclein (hαSyn) can cause accumulation of hαSyn oligomers, forming Lewy bodies, resulting in familial and sporadic PD. Although hαSyn has been found to interact with exocytotic machinery, little is known about how hαSyn replication or pathogenic mutation may regulate fusion pore kinetics during catecholamine release. Here, we used single-vesicle amperometry to detect the real-time exocytotic events in PC12 cells overexpressing control, hαSyn, or the pathogenic mutant (hαSyn-A53T). First, we found that upon KCl depolarization, cells overexpressing hαSyn or hαSyn-A53T decreased secretion rate compared to the control. In addition, we analyzed two forms of exocytotic events detected in amperometric recordings, i.e., full-fusion (FF) and kiss-and-run (KR) events. We found that hαSyn-A53T significantly increased the fraction of KR events compared to hαSyn, suggesting that hαSyn-A53T may preferentially increase the release from KR fusion pores. Moreover, by analyzing the spike characteristics of individual FF events. We found that hαSyn-A53T decreased peak amplitude and prolonged spike half-width, decay time, and whole duration compared to hαSyn. By contrast, the whole event area (proportional to the total released amount of catecholamines) was not changed by hαSyn or hαSyn-A53T compared

to the control, suggesting that hαSyn-A53T may prolong catecholamine release, without altering the amount released. With further analysis of the prespike foot (PSF), representing the initial fusion pore followed by full fusion, we found that the PSF duration was significantly increased by hαSyn or hαSyn-A53T compared to the control. According to the proposed kinetic model of fusion pores, we calculated the rate constants for fusion pores towards closure ($k_c$) and dilation ($k_d$). Both hαSyn and hαSyn-A53T decreased $k_c$ to a similar level (70%) compared to control. By contrast, hαSyn reduced $k_d$ to 80% and hαSyn-A53T reduced $k_d$ to 60% compared to the control, suggesting that hαSyn-A53T may profoundly prevent fusion pores from dilation. Together, despite of secretion rate reduced by both hαSyn and hαSyn-A53T, the pathogenic mutant hαSyn-A53T may preferentially prolong catecholamine release and stabilize fusion pores. Thus, the polyploidy and mutation of αSyn may differentially regulate fusion pore kinetics during catecholamine release.

**Disclosures: P. Chen:** None. **C. Wang:** None.

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.16/C11

**Topic:** B.04. Synaptic Transmission

**Support:** Lundbeck Foundation Fellowship

**Title:** Characterization of functional vesicle pools in sensory enteroendocrine cells

**Authors:** A. SHAABAN[1], B. H. COOPER[2], ***C. IMIG**[1];
[1]Dept. of Neurosci., Univ. of Copenhagen, Copenhagen N, Denmark; [2]Dept. of Mol. Neurobio., Max Planck Inst. for Multidisciplinary Sci., Goettingen, Germany

**Abstract:** Enteroendocrine cells (EECs) are a heterogenous group of chemo- and mechanosensitive cells in the gut epithelium that transmit information from the gut to the central nervous system via the release of peptide hormones and neurotransmitters. Recent studies indicate that EEC subtypes regulate processes such as food reward and aversion (Bai et al., *eLife*, 2022), feeding behavior and gut motility (Hayashi et al., *eLife*, 2023), visceral pain and anxiety (Bayrer et al., *Nature*, 2023), or sodium appetite (Liu et al., *Science Advances*, 2023). Despite their role in mediating important physiological processes and behaviors, little is known about the cell biological and molecular mechanisms underlying stimulus-induced vesicle fusion, transmitter and peptide release, and signaling to neurons in specific EEC subtypes. To gain a better understanding of the functional organization of secretory vesicle pools in genetically identified EEC subtypes, we established and characterized an *in vitro* experimental workflow combining mouse genetics, 2D-monolayer cultures of mouse gut epithelium, and single-cell electrophysiology and electrochemistry. We anticipate that our approach will make it possible to

understand the molecular control underlying gut-brain-axis signaling by specific EEC subtypes in health and disease.

**Disclosures:** **A. Shaaban:** None. **B.H. Cooper:** None. **C. Imig:** None.

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.17/C12

**Topic:** B.04. Synaptic Transmission

**Support:** HHMI Grant GT14961

**Title:** Bridging form and function with advanced electron microscopy to gain further insights in human synapses

**Authors: *C. R. EDDINGS**[1], W. S. ANDERSON[2], D. NAUEN[3], S. WATANABE[1];
[1]Cell Biol., [2]Neurosurg., [3]Pathology, Johns Hopkins Sch. of Med., Baltimore, MD

**Abstract:** Neurons maintain seamless signaling by recycling presynaptic components through endocytosis. In *C. elegans* neuromuscular junctions and mouse hippocampal neurons, this process is mediated by clathrin-independent 'ultrafast endocytosis'. However, it is unclear whether this ultrafast mechanism is conserved in the human brain. Being blind to the morphological changes occurring within human synapses as they communicate is detrimental to our understanding of typical and dysfunctional brain states. Determining if ultrafast endocytosis is a conserved process will contribute novel insight into the field of human neurobiology. To explore this mechanism, we use live human neocortex slices, extracted from patients who have undergone epilepsy surgery. We have adapted an advanced electron microscopy (EM) technique, 'zap-and-freeze' EM typically used with cultured cells, for use with these intact human brain slices. Zap-and-freeze EM utilizes electric field stimulation and high-pressure freezing to visualize synaptic membrane trafficking dynamics with high temporal and spatial resolutions (milliseconds and nanometers). Our use of intact brain tissue (i.e. resected cortical areas that are removed to access deeper hippocampal seizure locations) allows for more 'native' results—as the synapses are known to be established coming from an adult human brain and situated within an intact parenchyma allowing for natural cytoarchitectures. Using our technique, we have discovered that ultrafast endocytosis is recycling synaptic vesicles in human cortices (n=2, 30-year old male patients). We are currently investigating the endocytosis dynamics of different synapse types (excitatory/inhibitory) that are situated in the same brain slice. Our eventual goals are to expand into testing aged and diseased brains—offering unique data about the functionality and ultrastructure of synapses that are the best of both electrophysiology and electron microscopy worlds.

**Disclosures:** **C.R. Eddings:** None. **W.S. Anderson:** None. **D. Nauen:** None. **S. Watanabe:** None.

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.18/C13

**Topic:** B.04. Synaptic Transmission

**Support:** SCHO 820/4–6
DI853/3-5&7
SFB1089
SPP1757
INST1172 15

**Title:** The spatial organization of synaptic proteins in mammalian synapses and Drosophila NMJs detected by two-photon polarization microscopy

**Authors: *M. GALKOV**[1], K. PATIL[3,5,6], G. TAVOSANIS[3,5,6], M. FUHRMANN[4], D. DIETRICH[2], S. SCHOCH[1];
[1]Dept. of Neuropathology, [2]Dept. of Neurosurg., Univ. Hosp. Bonn, Bonn, Germany; [3]Dynamics of Neuronal Circuits, [4]Neuroimmunology and Imaging Group, German Ctr. for Neurodegenerative Dis. (DZNE), Bonn, Germany; [5]The Life and Med. Sci. Inst. (LIMES), Univ. of Bonn, Bonn, Germany; [6]Inst. for Developmental Biol., RWTH Aachen Univ., Aachen, Germany

**Abstract:** In recent years, the progress has been made in resolving the ultrastructure of the presynaptic cytomatrix. However, we still lack a detailed understanding of the 3-D organization of individual active zone (AZ) members. In this study, we aimed to investigate the spatial orientation of AZ proteins using the effect of linear dichroism (LD) detected by two-photon polarization microscopy. We validated our approach by demonstrating high LD in methoxy-X04 stained amyloid plaques and in a membrane-bound eGFP variant expressed in HEK293T cells and primary neurons. We also fused the actin filament reporter LifeAct to eGFP via several linkers and found that even non-structured linkers provide clear LD. Moreover, we next inserted the membrane-bound eGFP in neurexin1α to target the construct to synapses and showed that the reliable LD can be registered in the presynaptic membrane as well. Then LD was measured in synapses of cultured mouse primary neurons and in Drosophila larval NMJs expressing key AZ proteins fused with eGFP via non-structured linkers. We did not observe LD for the tested AZ proteins and also proved that LD is not disturbed by the eGFP-tagged protein molecules that are not integrated into the AZ cytomatrix. Thus, the regular spatial orientation of the AZ proteins can be excluded. However, certain radial regularities of their arrangements would remain undetected. Our data form the basis for further analyses aiming at resolving the spatial orientation of AZ members.

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

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

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**Topic:** B.04. Synaptic Transmission

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1U19NS107616-02
R01DA040484-04
R01MH071739-15
P01NS074972

**Title:** Functional specialization of hippocampal somatostatin-expressing interneurons

**Authors: G. G. GRANT**[1], *S. CHAMBERLAND[1], R. P. MACHOLD[1], E. R. NEBET[1], G. TIAN[1], M. HANANI[1], K. KULLANDER[2], R. W. TSIEN[1];
[1]New York Univ., New York, NY; [2]Uppsala Univ., Uppsala Univ., Uppsala, Sweden

**Abstract:** Hippocampal somatostatin-expressing (*Sst*) GABAergic interneurons (INs) exhibit considerable anatomical and functional heterogeneity. Recent single cell transcriptome analyses have provided a comprehensive *Sst*-IN subtype census, a plausible molecular ground truth of neuronal identity whose links to specific functionality remain incomplete. Here, we designed an approach to identify and access subpopulations of *Sst*-INs based on transcriptomic features. Four mouse models based on single or combinatorial Cre- and Flp- expression differentiated functionally distinct subpopulations of CA1 hippocampal *Sst*-INs that largely tiled the morpho-functional parameter space of the *Sst*-INs superfamily. Notably, the *Sst;;Tac1* intersection revealed a population of bistratified INs that preferentially synapsed onto fast-spiking interneurons (FS-INs) and were both necessary and sufficient to interrupt their firing. In contrast, the *Ndnf;;Nkx2-1* intersection identified a population of oriens lacunosum-moleculare (OLM) INs that predominantly targeted CA1 pyramidal neurons, avoiding FS-INs. Overall, our results provide a framework to translate neuronal transcriptomic identity into discrete functional subtypes that capture the diverse specializations of hippocampal *Sst*-INs.

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**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.20/C15

**Topic:** B.04. Synaptic Transmission

**Support:** Grant SCHO 820/4–6
Grant DI853/3-5&7
Grant SFB1089
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Grant INST1172 15

**Title:** More Efficient Synaptic Vesicle Release With Smaller Active Zone Protein Complexes

**Authors: *P. NEMCOVA**[1], H. BECKERT[3], M. GALKOV[2], S. SCHOCH[2], D. DIETRICH[1]; [1]Dept. of Neurosurg., [2]Dept. of Neuropathology, Univ. Clin. of Bonn, Bonn, Germany; [3]Med. Fac., Univ. of Bonn, Bonn, Germany

**Abstract:** The efficiency of vesicular neurotransmission depends on a complex interaction of presynaptic proteins in the so-called presynaptic active zone with each other and with vesicular and membrane proteins. Details of those interactions determine the fundamental properties of neurotransmission and information storage in the brain. Interactions of active zone proteins are still incompletely understood as their spatial arrangement and stoichiometry in the mammalian synapse are only partially revealed. In this work, we compare the distribution and amount of presynaptic proteins between functionally very distinct cerebellar synapses: very efficient climbing fiber synapses (cfs) showing a high release probability and low efficient parallel fiber synapses (pfs) characterized by a low release probability. We established quantitative volume electron microscopy (FIB-SEM) of phosphotungstic acid (PTA)-stain tissue. PTA is known to reveal a regular grid of protein complexes, so-called dense projections, likely containing high concentrations of active zone proteins. These dense projections were reported to have a stereotypical appearance across many synapse types and species. Our results show that dense projections strikingly differ between cfs and pfs: The more efficient cfs contain thinner, smaller, and fewer (per active zone area) dense projections compared to the less efficient pfs. We estimate that each dense projection of cfs contain ~25 MDa of active zone proteins whereas individual dense projections of less efficient pfs show a ~2-fold higher protein content (~50 MDa). The data show that dense projections substantially differ between types of synapses and indicate that their composition and/or stoichiometry reflects functional specialization. Moreover, the results shine new light on the role of the amount and distribution of presynaptic proteins as they suggest that highly efficient neurotransmission correlates with a smaller amount of active zone proteins.

**Disclosures: P. Nemcova:** None. **H. Beckert:** None. **M. Galkov:** None. **S. Schoch:** None. **D. Dietrich:** None.

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.21/C16

**Topic:** B.04. Synaptic Transmission

**Support:** MOE2017-T3-1-002
MOH-000225

**Title:** Synapsins support frequency-independent synaptic transmission at Purkinje cell-deep cerebellar nuclei neuronal synapses

**Authors: *J. KIM**, G. J. AUGUSTINE;
Lee Kong Chian Sch. of Med. - NTU, Singapore, Singapore

**Abstract:** During repetitive activity, most synapses exhibit a gradual run-down in their efficacy. This synaptic depression typically depends on the frequency of activity, with more depression occurring at higher frequencies. One notable exception is found in the cerebellum: synapses between Purkinje cells (PCs) and deep cerebellar nucleus (DCN) neurons exhibit frequency-independent transmission that allows this synapse to follow high-frequency activation faithfully by maintaining constant synaptic strength (Cell Rep. 17:3256). Synapsins are a family of synaptic vesicle proteins that are involved in clustering and mobilization of synaptic vesicles for exocytosis (Mol. Cells 38:936). Here we examined the role of synapsins in frequency-independent transmission by recording inhibitory postsynaptic currents (IPSCs) from DCN neurons while electrically stimulating axons of presynaptic PCs in cerebellar slices from synapsin triple-knockout (TKO) mice and control triple wild-type (TWT) mice. In the absence of synapsins, IPSC amplitude was not sustained during prolonged stimulation (10-100 Hz). In particular, there was more synaptic depression at higher frequencies of stimulation in TKO mice compared to TWT mice. By measuring the total amount of synaptic charge evoked by stimulation (J. Neurosci. 36:6742), we calculated that the rate of vesicle mobilization was significantly reduced in TKO mice (19 ± 9 pC/s) in comparison to TWT mice (78 ± 18 pC/s), while the size of the readily releasable pool (RRP) was similar in both genotypes. These results indicate that synapsins play an important role in maintaining frequency-independent transmission at PC-DCN synapses via enhancing vesicle mobilization during synaptic activity. To determine whether synapsins participate in the short-term synaptic facilitation that also significantly contributes to frequency-independent transmission at PC-DCN synapses (Nature 551:503), we examined synaptic transmission when external calcium concentration was lowered (from 1.5 to 0.5 mM) to reduce release probability and minimize synaptic depression. In TWT mice, this unmasked a synaptic facilitation that increased transmission up to 2-fold during repetitive stimulation. Surprisingly, this facilitation was completely absent in TKO mice. Our results indicate that synapsins are important for the persistence of transmission at PC-DCN synapses and work by regulating both synaptic vesicle mobilization and synaptic plasticity.

**Disclosures: J. Kim:** None. **G.J. Augustine:** None.

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR005.22/C17

**Topic:** B.04. Synaptic Transmission

**Support:** NIH Grant 5RO1NS111749

**Title:** Removing the Gβγ- SNAP25 brake on exocytosis exposes sexual dimorphisms in metabolic and thermal regulation systems

**Authors: *M. YOUNG**;
Pharmacol., Vanderbilt Univ., Nashville, TN

**Abstract: SFN Abstract:**
**Title**: Removing the Gβγ - SNAP25 brake on exocytosis exposes sexual dimorphisms in metabolic and thermal regulation systems
**Authors:** Montana Young, Ryan P. Ceddia, Analisa Thompson Gray, Zack Zurawski, Dianxin Liu, Julio E. Ayala, Owen P. McGuinness, Sheila Collins, Heidi E. Hamm **Abstract:** Regulation of neuronal exocytosis directs countless physiological processes in mammals, but the sex differences between males and females is under-appreciated in contemporary biomedical research. The Hamm laboratory has previously developed a mouse model that expresses a truncated form of SNAP25 (a key component of the SNARE complex) thereby preventing the inhibition of vesicular exocytosis via Gβγ - SNARE interaction. Utilizing this SNAP25α3 mouse model, we have observed significant phenotypical differences between homozygous male and female mice when environmental temperature is increased. We have previously shown both male and female SNAP25α3 mice display markedly increased insulin sensitivity, protection against diet induced obesity, and increased white adipose tissue beiging. However, this phenotype is abolished – only in males – when the mice are housed at thermoneutrality. We hypothesize that this difference in hypothalamic temperature regulation is tightly correlated with the estrous cycle, and this central nervous system effect is translating to the innervated adipose tissue of female SNAP25α3 mice. This temperature independent phenotype poses the Gβγ-SNARE interaction as a prime cellular mechanism to investigate the convergence of the nervous system and metabolic homeostasis, as well as sexual dimorphism in thermal regulation. To unpack this, we plan to conduct *in-vivo* metabolic studies with SNAP25α3 ovariectomized female mice compared to intact wild-type and intact SNAP25α3 females in standard room temperature (22° C) housing as well as thermoneutral (30° C) housing. We aim to correlate the metabolic and tissue architectural changes between the ovariectomized and intact SNAP25α3 females with the presence of the estrous cycle. These changes will be apparent through diet induced obesity, glucose tolerance, uncoupling protein 1 (UCP1), and adipose tissue beiging.

**Disclosures: M. Young:** None.

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.23/C18

**Topic:** B.04. Synaptic Transmission

**Support:** NIH Grant MH104536
NIH Grant NS117588

**Title:** Defining Functional Properties and Molecular Mechanisms Contributing to Synaptic Diversity Between Drosophila Tonic and Phasic Motoneurons

**Authors:** S. JETTI[1], A. B. CRANE[2], Y. AKBERGENOVA[2], ***J. T. LITTLETON**[3];
[1]MIT, [3]The Picower Inst. for Learning and Memory, [2]MIT, Cambridge, MA

**Abstract:** Synapses exhibit striking diversity in morphology, release probabilities, response kinetics, and short-term plasticity. Although extensive progress has been made in characterizing the molecular machinery of synaptic transmission, the range of mechanisms that generate functional synaptic diversity across neuronal subpopulations is still being elucidated. To begin addressing this question, we focused on two neuronal populations, tonic and phasic glutamatergic motoneurons (MNs), that innervate Drosophila larval abdominal muscles. Tonic Ib and phasic Is MNs show diversity in synaptic connectivity, bouton organization, dendritic patterning, intrinsic excitability, and release properties, providing an attractive neuronal subpopulation to characterize molecular and structural differences that contribute to these features. Gal4 drivers specific for each MN subtype were used to genetically label or manipulate them to characterize differences in synaptic transmission using optogenetics, electrophysiology, and quantal imaging. Is synapses displayed enhanced calcium influx, higher synaptic strength, and greater release probability per active zone (AZ) than Ib synapses, consistent with prior studies. Stimulated emission depletion (STED) nanoscopy and transmission electron microscopy (TEM) analyses revealed Ib and Is AZs show differences in nanoscopic organization, AZ area, T-bar length, and synaptic vesicle size and distribution that likely contribute to differences in their synaptic output. To investigate molecular mechanisms contributing to differences in synaptic strength and AZ organization, isoform Patch-Seq RNA profiling of the two glutamatergic motoneuronal subtypes and their postsynaptic muscle targets was performed. Genetic analysis identified distinct synaptic properties that mapped onto gene expression differences for several cellular pathways, including signaling ligands, cytoskeletal organization, membrane trafficking, post-translational modifications (PTMs), and intracellular calcium buffers. Differential PTMs (sialylation and ubiquitination) were also found to regulate Ib or Is NMJ growth and AZ structure in a synapse-specific manner. These data identify differences in AZ organization, transcriptomes, and PTMs that contribute to functional synapse diversity at Drosophila larval NMJs.

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**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR005.24/C19

**Topic:** B.04. Synaptic Transmission

**Support:** DFG 958

**Title:** Synaptotagmin-7 primes/docks synaptic vesicles via its C2A domain and regulates release probability

**Authors: *B. BOUAZZA AROSTEGUI**, S. T. ZOBEL, T. TRIMBUCH, C. ROSENMUND; Inst. for Neurophysiol., Charite Universtätsmedizin Berlin, Berlin, Germany

**Abstract:** The synaptic vesicle (SV) protein Synaptotagmin-1 (Syt1) docks/primes SVs and forms part of the $Ca^{2+}$-dependent vesicle translocation machinery that enables fast neurotransmitter release. Studies that combined genetic deletion with site-directed mutations suggest that Synaptotagmin-7 (Syt7) has overlapping yet partially independent functions to Syt1, but how Syt7 exert those functions remains poorly understood. To investigate the putative redundant role of Syt1/Syt7 in vesicle docking we performed high-pressure freezing and electron microscopy on hippocampal cultures from Syt1/7 double knockout and Syt7 knockout mice. We find that Syt7, similarly to Syt1, supports docking function. Syt1/Syt7 functional redundancy in priming and exocytosis of SVs were examined using electrophysiological recordings on excitatory hippocampal autaptic neurons. Supporting previous findings, Syt1/Syt7 both supported SV priming and clamping of spontaneous release in a redundant fashion. The lentiviral rescue experiments of Syt7 carrying charge-neutralizing and membrane-binding mutations located at distinct regions of its C2 domains also demonstrated that these functions are lost upon mutating the putative $Ca^{2+}$-binding site of the C2A but not the C2B domain. We found no evidence that Syt7 supports slow or fast $Ca^{2+}$-triggered release. Controlled coexpression experiments of Syt1 and Syt7 showed that release probability was inversely correlated to the relative expression levels of Syt7, arguing that Syt7 may outcompete Syt1 in its $Ca^{2+}$-triggering function. Based on these results we conclude that Syt7 regulates release probability and short-term plasticity by acting as a competitive antagonist against Syt1 rather than as a high-affinity sensor for asynchronous release.

**Disclosures: B. Bouazza Arostegui:** None. **S.T. Zobel:** None. **T. Trimbuch:** None. **C. Rosenmund:** None.

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.25/C20

**Topic:** B.04. Synaptic Transmission

**Support:** NINDS/NIA 2RF1 NS078165-12
MI 2104
SFB1286/B10

**Title:** Excess phosphoserine-129 α-synuclein induces synaptic vesicle trafficking and de-clustering defects at a vertebrate synapse

**Authors: *J. N. WALLACE**[1], Z. C. CROCKFORD[1], C. ROMÁN-VENDRELL[1], E. B. BRADY[1], C. HOFFMAN[3,2], K. J. VARGAS[1,4], M. POTCOAVA[5], S. T. ALFORD[5], D. MILOVANOVIC[3,2], J. R. MORGAN[1];
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**Abstract:** α-Synuclein is a presynaptic protein that normally regulates synaptic vesicle (SV) exocytosis and endocytosis. In Parkinson's disease (PD), α-synuclein aberrantly accumulates throughout neurons, including at synapses. During neuronal activity, α-synuclein is reversibly phosphorylated at serine 129, which modulates synaptic transmission and plasticity. While pS129 α-synuclein (pS129) comprises ~4% of total α-synuclein under physiological conditions, it dramatically increases ten- to twenty-fold in diseased brains. However, the impacts of excess pS129 on synaptic function are currently unknown. We show here that wild-type (WT) and pS129 have similar lipid binding profiles with selectivity for lipids enriched in synaptic membranes. Compared to WT, pS129 exhibits increased binding and oligomerization on synaptic membranes *in vitro* and enhances SV clustering in vesicle turbidity assays, suggesting they may produce different effects at synapses. To test this, pS129 was acutely injected into reticulospinal axons of sea lamprey (*Petromyzon marinus)*, a vertebrate with particularly large synapses (1-2 μm) that are amenable to detailed ultrastructural analyses using light and electron microscopy. When injected, recombinant human WT and pS129 α-synuclein robustly localized to lamprey synapses, as shown by colocalization with SV2. Without stimulation, pS129 caused no appreciable changes to synapses at the ultrastructural level. In contrast, stimulated synapses (20 Hz) injected with excess pS129 had a significant loss of SVs, partially compensated by an increase in putative endosomes (cisternae) and plasma membrane. pS129 did not alter the number of clathrin coated pits or vesicles, unlike WT α-synuclein which consistently impairs clathrin-mediated SV endocytosis. Additionally, pS129 caused a significant loss of total synaptic membrane, potentially explained by the dispersion of SVs away from the synaptic vicinity. Some small bundles of SVs were observed stretching away from the active zone, suggesting that pS129 crosslinks SVs in so-called 'microclusters'. A nearest neighbor analysis revealed that excess pS129 induced greater SV declustering compared to WT α-synuclein and controls. Live imaging further revealed slower FM destaining kinetics with pS129, consistent with impaired vesicle cycling. Thus, excess pS129 caused an activity-dependent inhibition of synaptic vesicle trafficking via altered SV clustering. This work suggests that accumulation of pS129 at synapses in diseased states could have profound effects on SV dynamics.

**Disclosures:** **J.N. Wallace:** None. **Z.C. Crockford:** None. **C. Román-Vendrell:** None. **E.B. Brady:** None. **C. Hoffman:** None. **K.J. Vargas:** None. **M. Potcoava:** None. **S.T. Alford:** None. **D. Milovanovic:** None. **J.R. Morgan:** None.

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.26/C21

**Topic:** B.04. Synaptic Transmission

**Support:** NIH Grant DC012938

**Title:** Increased density of active zone material and synaptic vesicles correlates with shortened synaptic delay during calyx of Held development

**Authors: *R. SHANKAR**[1], A. DAGOSTIN[2], G. PERKINS[3], D. JACKSON[1], G. SPIROU[1], H. VON GERSDORFF[2];
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**Abstract:** Globular bushy cells (GBCs) located in the ventral cochlear nucleus (VCN) extend axons innervating principal neurons (PNs) of the medial nucleus of the trapezoid body (MNTB), forming the largest terminal in the mammalian brain called the calyx of Held (CH). Early in development, MNTB PNs receive exuberant innervation, with most synapses located on the dendrites, followed by a rapid growth phase (postnatal day (P)2-4) where protocalyces form with a surface area covering half of the PNs soma. By P6 about 75% of MNTB PNs are innervated by a single CH. After hearing onset; in mice opening of the ear canal occurs at P10-12, the CH undergoes a second major transformation, from a spoon-like structure with thin collaterals to a digitiform structure with fenestrations containing ~300 active zones (AZs) in an adult mouse. In this study, we leverage electron tomography (ET), to demonstrate that the CH undergoes ultrastructural modifications at AZs during development which eventually results in the formation of a fast and precise relay synapse. Two mice at each age: young at P12 and adults at P30 were processed and 300 nm-thick serial sections were collected for ET. Dual axis tomograms of CHs were collected from multiple cells in the medial high frequency region of the MNTB on a 300 kV scope and reconstructed using IMOD software. Seg3D software tools were used to segment and analyze the ultrastructure of the AZs. Only completely captured AZs within each tomogram were analyzed. At both ages, we observed multiple synaptic sites contained within each CH swelling. These AZs were recognized by the pre- and postsynaptic membrane curvature and the presence of postsynaptic densities (PSDs). SVs in direct apposition with the presynaptic membrane were determined as docked vesicles. At P12, an average of 4.5 (SD 2.8) vesicles per active zone were docked (n=6 AZs), whereas at P30, this number increased to 7.2 (SD 2.7) (n=24 AZs). This increase in docked vesicles is accompanied by an increase in other AZ material as evidenced by a decrease in “free space” available within a 40 nm radius

juxtaposed to the presynaptic membrane. Free space was defined as the volume devoid of any AZ material such as SVs, tethers, and other electron-dense objects. At P12, an average of 62.73% free space (n=9 AZs) was estimated whereas by P30, the free space available was only 35% free space (n=27 AZs). We propose that this decrease in free space constrains diffusion of $Ca^{2+}$ ions to reach $Ca^{2+}$ sensors and facilitate rapid transmission of signals with ultrashort synaptic delay between presynaptic $Ca^{2+}$ current and exocytosis.

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**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.27/C22

**Topic:** B.04. Synaptic Transmission

**Support:** NIH Grant R35 NS127219

**Title:** Effects of somatostatin on fusion pores in $Ca^{2+}$-triggered exocytosis

**Authors: *J. CHENG**, M. B. JACKSON;
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**Abstract:** Somatostatin, a peptide hormone that activates G protein-coupled receptors, is known to have inhibitory actions on the secretion of many other hormones. In this study, we employed amperometry recording to investigate the impact of somatostatin on $Ca^{2+}$-triggered exocytosis of catecholamine from mouse chromaffin cells. We analyzed individual fusion events (spikes) for various properties of fusion pores at different stages, including the permeability of late-stage fusion pores. We used two different stimulation protocols to induce exocytosis, high KCl and caffeine. In addition, fluorescence imaging with Oregon Green 488 BAPTA-1 was used to monitor the rise in free intracellular calcium following KCl or caffeine application. Our results show that while the spike frequency differs between the two induction methods, somatostatin reduced spike frequency in both circumstances. We observed prolonged pre-spike foot duration, increased spike rise time, and extended spike half-width in the presence of somatostatin, indicating that somatostatin slowed the initial and expanding phases of fusion pores. Furthermore, the permeability of fusion pores reaches a plateau during the late stage, and this plateau is not changed by somatostatin. Imaging showed no significant effect of somatostatin on fluorescence increases after stimulation, suggesting that the inhibitory effect was not caused by reducing the rise in intracellular free calcium. In conclusion, our results demonstrate that somatostatin influences the initial and expanding stages of fusion pores, while having no effect on late-stage fusion pores. These findings provide insights into the mechanism by which

somatostatin modulates exocytosis and enhance our understanding of the complex dynamics of cellular secretion.

**Disclosures: J. Cheng:** None. **M.B. Jackson:** None.

**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.28/C23

**Topic:** B.04. Synaptic Transmission

**Support:** NRF of Korea-2020R1A2C2010791

**Title:** Nsf is a fine regulator for synaptic vesicle exocytosis for synaptic persistence

**Authors: Y. JO**[1], S. HAN[2], S. RYU[1], *S. KIM[3];
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**Abstract:** Synaptic persistence relies on the maintenance of synaptic functionality through processes such as synaptic vesicle exocytosis and endocytosis. One crucial aspect of achieving this goal involves the assembly and disassembly of fusion machinery, such as the SNARE complex. The disassembly of the SNARE complex, facilitated by NSF (N-ethylmaleimide sensitive fusion protein), is particularly important for the next round of synaptic vesicle fusion. However, the specific physiological function of NSF at CNS synapses in this regard remains relatively unexplored. In this study, we aimed to investigate the physiological role of NSF in synaptic persistence. To accomplish this, we utilized a pHluorin-based assay combined with shRNA targeting NSF to monitor consecutive synaptic transmission and synaptic vesicle retrieval in neurons lacking NSF. Our findings revealed significant impairments in synaptic transmission and retrieval in neurons where NSF was knocked down (NSF-KD). Remarkably, repetitive stimuli in NSF-KD neurons led to the identification of three distinct synaptic phenotypes, indicating variations in exocytosis and endocytosis. Furthermore, the introduction of shRNA-resistant NSF cDNA effectively restored the physiological diversity observed in NSF-KD neurons. These results demonstrate that NSF is necessary for both synaptic transmission and retrieval, highlighting its role in fine-tuning the functional variabilities of synapses for synaptic persistence.

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**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR005.29/C24

**Topic:** B.04. Synaptic Transmission

**Support:** NIH Grant DC014093
NIH Grant TR004161

**Title:** Elucidating the role of presynaptic $\alpha_2\delta$1-3 proteins in the regulation of synaptic function

**Authors: *W. MILANICK**[1,2,3], M. AL-YAARI[2], C. THOMAS[5], D. GUERRERO-GIVEN[5], N. KAMASAWA[5], S. M. YOUNG, Jr[2,4];
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**Abstract:** Synapses are the fundamental unit of information transfer in the central nervous system (CNS) and are composed of highly complex molecular machinery that tightly regulates synaptic transmission and neuronal circuit output. The $\alpha_2\delta$ proteins ($\alpha_2\delta$1-4) are extracellular proteins initially identified as auxiliary subunits of voltage-gated $Ca^{2+}$ ($Ca_V$) channel complexes. Mutations in $\alpha_2\delta$1-4 are linked to a wide range of disorders, including neuropathic pain and epilepsy, and $\alpha_2\delta$1-2 are targeted by drugs used to treat these disorders. Multiple roles have been described for the $\alpha_2\delta$ isoforms in independently regulating synaptic function and $Ca_V$ channel complexes. Many CNS synapses contain a mixture of $\alpha_2\delta$1-3, which are found in both the pre and postsynaptic compartments, with $\alpha_2\delta$4 mainly restricted to the retina. Currently, studies of $\alpha_2\delta$ are mostly done using global mutant/knockout (KO) models or in cell culture. While powerful, these studies prevent conclusions on the presynaptic functions of $\alpha_2\delta$ in an *in vivo* circuit. To elucidate the presynaptic regulatory roles of $\alpha_2\delta$1-3 in a native neuronal circuit, we developed a novel $\alpha_2\delta$1-3 conditional KO mouse model and ablated $\alpha_2\delta$1-3 at the calyx of Held, a large glutamatergic axosomatic synapse in the lower auditory brainstem. Using this animal model, we ablated all three isoforms using a Helper-Dependent Adenovirus that expresses Cre recombinase at postnatal day 1. Subsequently, using a multidisciplinary approach, we analyzed how loss of $\alpha_2\delta$1-3 at the adult-stage (P18 onwards) calyx of Held impacted synaptic function. Results will be discussed.

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**Poster**

**PSTR005. Presynaptic Mechanisms, Organization, and Structure**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR005.30/C25

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

**Support:** R01 MH50712
R01 NS103938

**Title:** Synaptic vesicle lipid composition regulated by Phospholipid Flippase ATP8A1 confers neurotransmitter release at high frequency

**Authors: *H. XU**[1], J. OSES-PRIETO[2], R. H. EDWARDS[1];
[1]Departments of Physiol. and Neurol., Univ. of California San Francisco Sch. of Med., San Francisco, CA; [2]Univ. of California San Francisco, San Francisco, CA

**Abstract:** Synaptic vesicle lipid composition regulated by Phospholipid Flippase ATP8A1confers neurotransmitter release at high frequency
Hongfei Xu[1], Juan A. Oses-Prieto[2], and Robert H. Edwards[1]
[1]Departments of Physiology and Neurology, UCSF School of Medicine, San Francisco, CA
The nervous system encodes information through the timing and frequency of neuronal firing. To convey information about timing, synapses rely on the speed and synchrony of neurotransmitter release. To convey information about frequency, synapses must release neurotransmitter in a graded manner over the range of firing frequencies. These two modes of signaling require different machinery because the fast, synchronous release tends to produce synaptic depression due to synaptic vesicle (SV) depletion, limiting the ability to release with repeated stimulation and particularly at high frequency. Conversely, a more linear response to firing rate requires a small synchronous response in response to a single action potential, which limits information about timing. These mechanisms enable synapses to decode information stored in the pattern of firing. Synapses that depress in response to repeated stimulation are generally considered to have a high release probability that results in SV depletion. In contrast, synapses that facilitate are thought to have a low initial release probability that requires stimulation at high frequency. This model presumes that all the synaptic vesicles in an individual neuron are homogeneous and hence differ only in their position along a single pathway to exocytosis. However, SVs are generally considered to recycle either directly from the plasma membrane or from endosomes by adaptor protein AP-3. How these two biogenesis pathways contribute the properties of SVs are still unclear. In this study, the use of pH-sensitive GFP variant ecliptic pHluorin-based reporters has enabled us to identify a subpopulation of SVs that responds specifically to high firing rates. VAMP7-pH labels this SV subpopulation and consistent with a role for AP-3 in its production, loss of AP-3 selectively impairs the response of VAMP7-pH at high frequency. In contrast, VGLUT2-pH labels a population of SVs that responds to low frequency stimulation, depresses at high frequency and does not depend on AP-3. Proteomics reveals that AP-3 targets phospholipid flippase ATP8A1 to SVs, and loss of ATP8A1 recapitulates the defect in SV mobilization at high frequency observed with loss of AP-3. The mechanism involves recruitment of synapsin by the cytoplasmically oriented phosphatidylserine translocated by ATP8A1. Thus, ATP8A1 enables this subset of SVs made by AP-3 to release at high frequency.

**Disclosures: H. Xu:** None. **J. Oses-Prieto:** None. **R.H. Edwards:** None.

**Poster**

**PSTR006. Synaptic and Spike-Timing Dependent Plasticity**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR006.01/C26

**Topic:** B.05. Synaptic Plasticity

**Title:** Effect of a lognormal spike timing dependent plasticity rule on cell assembly capacity in spiking neural networks

**Authors: *D. ARTHUR**, E. ALBERS, M. TATSUNO;
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**Abstract:** Estimation of the storage capacity of the brain's neural circuits is one of the important neuroscience questions. It has been hypothesized that temporally coordinated neurons, or cell assemblies (CAs), represent mental or perceptual entities. Thus, evaluation of the number of CAs is key to answering this question. Previous modeling studies using a spiking neural network with axonal conduction delays and the add spike-timing-dependent plasticity (add-STDP) rule have shown that many more CAs than that of the Hopfield nets were detectable (Izhikevich, 2006). One limitation of this study was its focus on a single network structure, the cortex. Another significant limitation of this study is the unrealistic, bimodal distribution of connection weights that results from the add-STDP rule. In the real brain, the synaptic connection weights are known to be distributed lognormally both globally (all synapses) and locally (synapses for single neurons). Thus, we have implemented a lognormal spike-timing-dependent plasticity rule (log-STDP, Gilson & Fukai, 2011) into networks of Izhikevich spiking neurons inspired by the cortex and hippocampal CA1 region. First, we verified that a global lognormal distribution of the synaptic weights was achieved in both the cortex and hippocampal CA1 simulations. As for the local synaptic weight distributions surrounding single neurons, we found that they trend toward skewed, heavy-tailed distributions in the hippocampal CA1 simulations but not for the cortex simulations. Next, we detected CAs in the Izhikevich nets using the unsupervised method proposed by Russo and Durstewitz (2017). We found that the log-STDP rule produced more cell assemblies in the cortex simulations than add-STDP. However, in the hippocampal CA1 simulations, far fewer assemblies were produced, and those simulations with the add-STDP rule produced more than the log-STDP rule. The main difference between the cortex and hippocampal CA1 simulations is the number of recurrent excitatory connections. Therefore, these simulation results suggest that the cell assembly capacity of spiking neural networks is related to the number of excitatory-to-excitatory connections in the network.

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**Poster**

**PSTR006. Synaptic and Spike-Timing Dependent Plasticity**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR006.02/C27

**Topic:** B.05. Synaptic Plasticity

**Support:** Israel Science Foundation Grand 1745/18
Gatsby Charitable Foundation

**Title:** Exploring the relationship between adjacency and weighted motif statistics in plastic neural networks

**Authors: *E. TANANYAN**[1], Y. BURAK[2,1];
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**Abstract:** There are two main types of structures in the synaptic connectivity between neurons in the cortex: the first structure is essentially binary - the existence (or lack) of connections between any two neurons. It is believed that this adjacency structure is determined, to a large extent, by the geometrical arrangement of the dendrites and axons, and is relatively stable over time. The second form of synaptic structure involves the strength of synaptic connections between neurons. These weights are subject to change through neural activity-induced plasticity mechanisms. To understand the structure of neural networks in the brain, it is important to develop an understanding of the interplay between the statistics of the two structures. In this work, we aim to provide first steps toward this goal. We examine the statistics of sub-graphs of the network (motifs), quantified by measures called motif strengths, and develop a self-consistent theory to approximate the dynamics of these statistical measures in networks of linear Poisson neurons, in which synapses are subject to spike timing dependent plasticity. Previously, this has been done for motifs that consist of up to two edges (G.K. Ocker, A. Litwin-Kumar, B. Doiron, PLoS Comput. Biol., 2020). Here we extend the previous work by considering also three edge motifs. The main challenge is that there are many more motifs to consider. Consequently, the task of deriving analytic equations for the dynamics of motif strengths, by hand, is impractical. To deal with this difficulty we developed a graphical method to derive a set of self-consistent equations, that can be implemented by a computer algorithm. We found that for some cases, like the fully connected case, both second and third order approximations give very accurate results, but in Erdős-Rényi networks with moderately sparse connectivity (e.g. $p = 0.5$), treating only second order motifs gave inaccurate predictions, while the self-consistent equations for motifs up to third order remained very accurate. In future work, we intend to extend the analysis to networks with other forms of adjacency statistics. In conclusion, our study has successfully developed an automated process to derive a closed self-consistent set of equations for motif strength dynamics. The model provides a set of analytic equations that can be solved numerically without the need to simulate the dynamics of individual synapses and are potentially amenable to further study using analytic tools.

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**Poster**

**PSTR006. Synaptic and Spike-Timing Dependent Plasticity**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

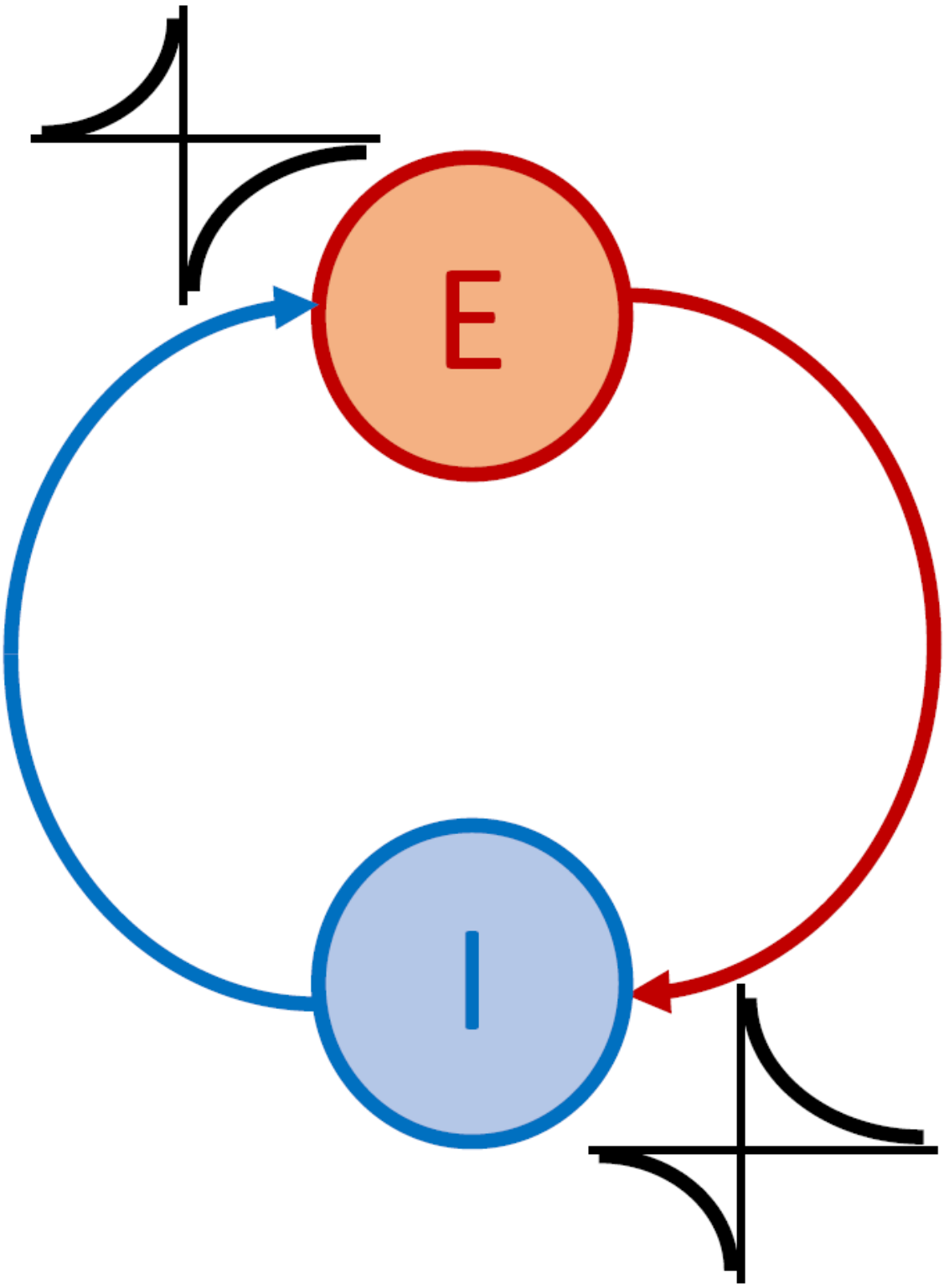
**Program #/Poster #:** PSTR006.03/C28

**Topic:** B.05. Synaptic Plasticity

**Title:** Spike-timing dependent plasticity (stdp) emerges from a direct data-driven controller (dd-dc) model of a neuron

**Authors: M. TOURNOY**[1], J. MOORE[3,2], T. TESILEANU[2], A. GENKIN[1], *D. CHKLOVSKII[4,5];
[1]Simons Fndn., NEW YORK, NY; [2]Flatiron Inst., Simons Fndn., New York, NY; [3]NYU Sch. of Med., New York, NY; [4]Ctr. for Computat. Neuroscience, Flatiron Inst., New York, NY; [5]Neurosci. Inst., NYU Med. Ctr., New York, NY

**Abstract:** Neurophysiological experiments have revealed that STDP is both ubiquitous and diverse. The specific STDP form, i.e. the dependence of synaptic weight variation on pre/post spike time lag, differs among synapses linking different cell types. Additionally, STDP form depends on the average firing rate.
While numerous theoretical and modeling studies on STDP exist, a normative theory accounting for STDP characteristics has yet to be established. Some aspects of STDP, such as the causal window (i.e. postsynaptic spike following presynaptic), can be understood as an extension of Hebbian plasticity in a spike-timing dependent context. However, other features, like the "anti-causal" window (i.e. presynaptic spike following postsynaptic), still remain paradoxical and in need of a functional explanation.
In this study, we demonstrate that many characteristics of STDP naturally emerge from a novel approach that models neurons as feedback controllers responsible for stabilizing synaptically linked loops of neurons. To formulate a biologically plausible model of a neuron as a controller, we employ the recently developed DD-DC methodology in which the neuron implicitly identifies the dynamics of the rest of the loop and optimizes control through the Linear Quadratic Regulator (LQR) formulation.
Our model provides an explanation for the "anti-causal" window of STDP because, in the presence of a feedback loop, a postsynaptic spike may traverse the loop and cause a presynaptic spike, effectively rendering the “anti-causal” window causal. Specifically, for synapses connecting inhibitory to excitatory (excitatory to inhibitory) neurons, our model predicts Hebbian (anti-Hebbian) STDP forms. The dependence of the metabolic costs of spiking on the cell type can be modeled by varying the LQR parameters resulting in the modulation of the synaptic plasticity rules. Furthermore, our model successfully reproduces the dependence of the STDP form on the average firing rate.
Overall, our findings contribute to a deeper understanding of STDP and support modeling neurons using the DD-DC framework.




**Disclosures:** **M. Tournoy:** None. **J. Moore:** None. **T. Tesileanu:** None. **A. Genkin:** None. **D. Chklovskii:** None.

**Poster**

**PSTR006. Synaptic and Spike-Timing Dependent Plasticity**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR006.04/C29

**Topic:** B.05. Synaptic Plasticity

**Title:** Inhibition of deep brain stimulation evoked potentials by short-interval paired pulse or high frequency pulse train stimulation

**Authors: *R. SOROUSHMOJDEHI**[1], S. SEYYEDMOUSAVI[1], T. D. SANGER[1,2];
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**Abstract:** One of the effective surgical interventions that improves quality of life in patients with movement disorders such as dystonia is Deep Brain Stimulation (DBS). Despite recent advancements in clinical applications of DBS, the underlying mechanism of DBS is not yet well understood. It is hypothesized that a deficit of inhibition and abnormal plasticity within basal ganglia could be a key feature in the pathophysiology of dystonia.Previous studies have demonstrated that synaptic depression can be induced by paired pulse DBS with short interstimulus intervals (ISI) (between 20 to 40 msec). Moreover, another study indicated that DBS at 10 kHz produces clinical benefits in patients with movement disorders. However, these studies were mostly conducted on Parkinson's patients and the effect of high frequency stimulation on Evoked Potentials (EP) is still unknown.To test the effect of very short ISIs, we have conducted two protocols: the first study uses paired pulse DBS with ISIs 0.3, 0.5, 1, 3 and 5 msec applied to Globus Pallidus internal segment (GPi) of a dystonic patient. Paired pulse depression was evaluated by the ratio of EP followed by each pulse recorded from Ventral Oralis/Subthalamic Nucleus (VoSTN). We found that using ISIs less than 1 msec, EP due to the 2nd pulse is completely inhibited. The second protocol investigates the effect of high frequency stimulations such as 900 Hz by comparing the EP produced by a train of low frequency stimulations like 80 Hz before and after high frequency stimulation. The average EP of post-HFS detected in VoSTN showed less peak to peak amplitude compared with pre-HFS.Our results show that short inter-stimulus intervals produce a depression of evoked responses, both following paired pulse and following longer pulse trains, when the ISI is less than 1 msec. This suggests an inhibitory phenomenon that may be similar to what is seen in TMS paired pulse protocols. Further research is needed, but our results suggest the possibility of using this type of inhibition to change brain activity and potentially improve motor function in patients with movement disorders including dystonia.

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**Poster**

**PSTR006. Synaptic and Spike-Timing Dependent Plasticity**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR006.05/C30

**Topic:** B.05. Synaptic Plasticity

**Support:** CFI LOF 28331
CIHR PG 156223
FRSQ CB 254033
NSERC DG 2017-04730
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Healthy Brains Healthy Lives PhD Fellowship
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Integrated Program in Neuroscience Studentship

**Title:** Deciphering astrocyte signaling in neocortical timing-dependent long-term depression

**Authors: *C. GUO**[1,2,3], A. WATANABE[1,2,3], P. J. SJOSTROM[1,3,4];
[2]Integrated Program in Neurosci., [3]Ctr. for Res. In Neurosci., [4]Dept. of Med., [1]McGill Univ., Montreal, QC, Canada

**Abstract:** Information is stored in the brain by synaptic plasticity, which is elicited by specific neuronal activity patterns. For example, timing-dependent long-term depression (tLTD) is induced by the millisecond relative timing of pre- and postsynaptic spiking in connected neurons. In the tripartite synapse model, astrocytes play a crucial role in plasticity induction. However, it is unclear how astrocyte signaling — which occurs through intracellular calcium transients on a timescale of seconds — can meaningfully impact plasticity that operates on milliseconds. We therefore decided to decipher astrocyte signaling in tLTD. To verify the need for astrocytes in tLTD, we abolished astrocyte function with sodium fluoroacetate (NaFAC). Using quadruple patch clamp, we recorded from connected layer-5 pyramidal cells in postnatal day (P) 11-16 C57BL/6J mouse acute visual cortex slices. tLTD was induced by 20-Hz spiking pairings at $\Delta t$ = -25 ms timing difference. Compared to no-induction controls with and without NaFAC (after/before = 101% ± 3%, n = 14), unitary EPSPs depressed without (74% ± 6%, n = 7, $p < 0.01$) but not with NaFAC (103% ± 7%, n = 7, $p = 0.76$; all t-tests after ANOVA, $p < 0.01$; all p values were Bonferroni-Dunn *post-hoc* corrected). NaFAC alone did not cause EPSP rundown (103 ± 4%, n = 6, $p = 0.46$). Using 2-photon microscopy, cell morphologies with and without NaFAC were grossly indistinguishable. However, data inclusion rates were lower with NaFAC (13/31=42%) than without (15/23=65%, $p < 0.001$), suggesting that NaFAC affects plasticity experiments. However, this also demonstrates the critical role of astrocytes in synaptic transmission. Taken together, we conclude that tLTD depends on astrocytes. Since astrocytes likely signal via calcium to control tLTD, we imaged astrocyte calcium events across development to see when they matured. With age (n = 36 astrocytes), calcium signals became shorter ($r = -0.54$, $p < 0.001$), more frequent ($r = 0.63$, $p < 0.001$), and decorrelated ($r = -0.54$, $p < 0.01$). These properties stabilized at ~P15, i.e., after eye opening. Overall, our findings support the view that astrocytes govern tLTD. Precisely how slow astrocyte signaling can influence millisecond tLTD remains mysterious, which warrants further study.

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

**Poster**

**PSTR006. Synaptic and Spike-Timing Dependent Plasticity**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR006.06/C31

**Topic:** B.05. Synaptic Plasticity

**Support:** NSERC RGPIN-2020-05255

**Title:** The Influence of Astrocytes on Spike Timing-Dependent Plasticity in the Visual Cortex

**Authors: *Y. INGLEBERT**[1,2], R. SANZ GÁLVEZ[1,2], A. KOLTA[1,2,3];
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**Abstract:** Spike timing-dependent plasticity (STDP) is a type of synaptic plasticity that relies on the precise timing of pre- and post-synaptic activity. Conventionally, timing-dependent long-term potentiation (t-LTP) occurs when an excitatory post-synaptic potential (EPSP) is followed, after a few milliseconds, by one or more postsynaptic action potentials (APs). Conversely, timing-dependent long-term synaptic depression (t-LTD) is induced when an EPSP is preceded by one or more postsynaptic APs. STDP is a complex rule influenced by various factors, including specific activity patterns, neuromodulators, dendritic spikes or extracellular calcium ($Ca^{2+}$). Astrocytes, which can release gliotransmitters like D-Serine or glutamate, or locally modulate $Ca^{2+}$ levels, have control over these factors and can modulate synaptic transmission. However, the role of astrocytes in the STDP rule is still poorly understood and described. Moreover, recent findings show that the induction of t-LTP or t-LTD may not always be achievable *in vivo*, primarily because previous *in vitro* investigations were conducted under non-physiological circumstances, specifically involving non-physiological calcium levels. It is highly likely, therefore, that the STDP rule requires in addition to timing one or more factors to exist. Could astrocytes be the key to gate the induction of synaptic plasticity? Our recent findings have shown that stimulation of astrocytes near the soma of layer 5 pyramidal neurons, potentiated integration of subthreshold distal inputs, and prolonged the time window during which suprathreshold distal inputs can interact with proximal inputs, by overriding firing adaption evoked by distal inputs. This effect was mediated by S100β, a calcium-binding protein, which alters the extracellular level of $Ca^{2+}$. Here we further examine how extracellular $Ca^{2+}$ levels and astrocytic manipulations influence synaptic and axonal plasticity in layer 5 pyramidal neurons of the visual cortex. These findings will help increasing our understanding of how astrocytes contribute to neuronal computations in general and visual function specifically.

**Disclosures: Y. Inglebert:** None. **R. Sanz Gálvez:** None. **A. Kolta:** None.

**Poster**

**PSTR006. Synaptic and Spike-Timing Dependent Plasticity**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR006.07/C32

**Topic:** B.05. Synaptic Plasticity

**Support:** NIH intramural funds

**Title:** Hippocampal Kv4.2 complexes regulate metaplasticity and reversal learning

**Authors: *C. MALLOY**[1], J.-H. HU[4], J. GUTZMANN[2], A. PRATT[5], Y. LIU[3], D. A. HOFFMAN[3];
[1]NICHD, [3]NIH, [2]NIH, Bethesda, MD; [5]NICHD, [4]NICHD, Bethesda, MD

**Abstract:** The A-type potassium current ($I_A$) is a vital regulator of neuronal excitability and synaptic plasticity. In hippocampal CA1 pyramidal cells, this current is carried primarily by voltage-gated Kv4.2 K+ channels. Along with other voltage-gated ion channels localized in the somatodendritic compartment of pyramidal cells, Kv4.2 contributes to dendritic integration and excitability. Kv4.2 functions in a macromolecular complex together with the auxiliary subunits K+ channel interacting proteins (KChIPs) and DPLP(s) in the mouse hippocampus. Proper assembly and dynamic regulation of this complex is integral in facilitating its role in neuronal signal processing and plasticity. Using a TAP-mass spectrometry screen, we identified a molecular cascade involving p38 kinase-mediated Pin1 isomerization of a C-terminal motif in Kv4.2 as a crucial regulator of Kv4.2-DPP6 binding dynamics. To probe the role of this p38-Pin1 cascade in regulating the Kv4.2 complex and neuronal function, Crispr-cas9 technology was utilized to generate a knock-in mouse model (Kv4.2TA) with abolished p38 and Pin1-Kv4.2 binding. We have used whole-cell patch clamp electrophysiology to investigate the consequences of this impaired binding and loss of dynamic regulation on neuronal physiology and behavior. Kv4.2TA mice display reduced neuronal excitability which is traced to an increase in $I_A$ density in CA1 pyramidal neurons. In multiple behavioral tests of hippocampal-dependent learning and memory, Kv4.2TA mice demonstrated enhanced reversal learning, indicative of improved cognitive flexibility. To decipher the mechanisms underlying this enhancement in reversal learning, single-cell measures of spike timing-dependent long-term potentiation (STD-LTP) and long-term depression (LTD) were performed in CA1 pyramidal neurons in acute hippocampal slices. Intriguingly, while synaptic plasticity from basal state is preserved in Kv4.2TA mice relative to WT, a notable enhancement in the removal of STD-LTP (depotentiation magnitude) is observed in Kv4.2TA mice, suggestive of a synapse state-dependent difference in synaptic plasticity in hippocampal area CA1. Pharmacological manipulations during the induction of depotentiation have revealed a distinction in the mechanisms driving this metaplasticity in Kv4.2TA mice relative to WT. Investigations into how these mechanisms are linked to reversal learning are on-going. In sum, we have identified, for the first time, Kv4.2 and its regulation as a key modulator of metaplasticity and reversal learning in the hippocampus.

**Disclosures: C. Malloy:** None. **J. Hu:** None. **J. Gutzmann:** None. **A. Pratt:** None. **Y. Liu:** None. **D.A. Hoffman:** None.

**Poster**

**PSTR006. Synaptic and Spike-Timing Dependent Plasticity**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR006.08/C33

**Topic:** H.05. Working Memory

**Title:** Pkc dependent plasticity in the dorsal striatum: effect of glud1

**Authors: *P. B. CHETTIAR**[1], S. M. DRAVID[2];
[1]Pharmacol. and neuroscience, Creighton Univ., omaha, NE; [2]Pharmacol. and neuroscience, Creighton Univ., Omaha, NE

**Abstract:** Synaptic plasticity is a fundamental mechanism involved in modifying synaptic strength, which underpins learning, memory, and adaptive behaviors. While Protein Kinase C (PKC) has been widely recognized as a key regulator of synaptic plasticity across various brain regions, its role in the striatum - a critical region for motor and reward functions is yet to be fully understood. Although GluD2, a member of the ionotropic glutamate receptor family, is known to play a role in PKC-dependent plasticity at the PF-PC synapse, the specific contribution of GluD1, which is abundantly expressed in the striatum, remains relatively unexplored. Our research aims to investigate the role of GluD1 in PKC-dependent synaptic plasticity within the dorsal striatum. Our observations revealed distinct changes in excitatory post-synaptic currents (EPSC) mediated by NMDARs and AMPARs in GluD1 wild-type and knockout animals, highlighting the critical involvement of GluD1 in modulating synaptic activity. Upon PKC activation, we observed a reduction in the amplitude and frequency of NMDAR-mediated miniature EPSC (mEPSC) in both GluD1 WT and KO animals, while AMPA mEPSC remained unchanged in GluD1 WT, but increased in both amplitude and frequency in GluD1 KO animals. These findings suggest a critical role for GluD1 in modulating PKC-dependent changes in NMDAR and AMPAR-mediated activity. Building upon previous research emphasizing the role of the Ser945 residue in GluD2's C-terminal for PKC-dependent plasticity, we designed a 5-amino acid peptide targeting the analogous Ser944 residue in GluD1's C-terminal. Our results demonstrated that this peptide selectively reduced NMDAR-mediated EPSC in GluD1 WT but had no impact in GluD1 KO animals. These findings imply that the Ser944 residue in GluD1 may play a specific role in the regulation of NMDAR responses, potentially in a PKC-dependent manner. The findings shed light on the interplay between GluD1 and PKC in synaptic plasticity and highlight the potential utility of the designed peptide for selectively manipulating GluD1-dependent synaptic plasticity. Further research is needed to uncover underlying mechanisms and explore therapeutic applications arising from these findings.

**Disclosures: P.B. chettiar:** None. **S.M. Dravid:** None.

**Poster**

**PSTR007. Somatic and Dendritic Integration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR007.01/C34

**Topic:** B.06. Intrinsic Membrane Properties, Electrical Synapses, and Signal Integration

**Support:** R01NS123959

**Title:** Input-rate driven dendritic computations in pyramidal neurons during temporally complex patterns of excitation.

**Authors: *N. DEMBROW**[1], M. HUDSON[1], D. CONTRERAS[2], W. J. SPAIN[1];
[1]Physiol. and Biophysics, Univ. of Washington, Seattle, WA; [2]Neurosci., Univ. of Pennsylvania Perelman Sch. of Med., Philadelphia, PA

**Abstract:** Understanding how neurons encode synaptic input across a range of network activity regimes is essential to understanding how the brain processes information. For neocortical pyramidal neurons, integration is further complicated by the fact that they receive excitatory input onto spines distributed along dendritic branches. Local dendritic nonlinearities including NMDA-dependent branch "spikes" boost the response to spatially clustered and synchronous input. How this translates into the integration of complex patterns of ongoing activity remains unclear. To examine dendritic integration during such regimes, we utilize two-photon glutamate (2p-glu) uncaging to repeatedly activate multiple dendritic spines at random intervals. We previously reported that for the proximal dendrites of extratelencephalic (ET) layer 5 pyramidal neurons in the mouse motor cortex, spatially restricted synchrony is not a prerequisite for dendritic boosting. Instead, a model based on the total input rate onto a dendritic branch captured 2p-glu driven voltage responses to uncorrelated spine stimulations at a fixed mean Poisson rate. Here, we use this input-rate based model to make predictions and experimentally test how more complex patterns of activity engage NMDA-dependent branch spikes. Consistent with model predictions, experiments using 2p-glu stimulation show greater entrainment of the voltage response to slow (3 Hz) compared to fast (15 Hz) oscillations in mean input rate. Next, we tested how the proximal dendrites integrate stimuli that replicate network activity during the transition into slow wave sleep. VGLUT2 immunohistochemistry suggests that ~15% of excitatory synapses onto M1 L5 ET pyramidal neuron basal dendrites are of thalamic origin. We find that stimuli patterned from thalamocortical relay neuron burst firing observed in vivo during non-REM slow wave sleep onto 10-15% of targeted spines do not recruit supralinear voltage responses on their own, but when combined with the Poisson-distributed stimulation (to mimic cortical firing rates) they evoked NMDA spikes well-timed with the "thalamic-like" bursts. Finally, to assess how synaptic dynamics can shape branch integration, we included use-dependent synaptic dynamics (short-term depression and facilitation) in our model and stimulation regimes. Our model predicts that the dendritic branch supralinearity counteracts input rate gain normalization caused by synaptic depression and enhances the sensitivity to transient shifts in input rate. These results suggest that dendritic nonlinearities amplify certain patterns of synaptic input and thereby shape how neurons encode network activity.

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**Poster**

**PSTR007. Somatic and Dendritic Integration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR007.02/C35

**Topic:** B.06. Intrinsic Membrane Properties, Electrical Synapses, and Signal Integration

**Support:** US National Science Foundation (grant number 2223827)
Stanford Medical Center Development (Discovery Innovation Fund)
Stanford Institute for Human-Centered Artificial Intelligence (HAI)
Stanford WuTsai Neurosciences Institute
Stanford Graduate Fellowship

**Title:** On detecting a spatiotemporal pattern of spike activity in a stretch of dendrite

**Authors: *K. R. MAMA**[1], K. A. BOAHEN[2];
[1]Neurosciences, [2]Bioengineering, Stanford Univ., Stanford, CA

**Abstract:** While traversing through the natural world, we experience our surroundings as a continuous stream of information over time. This constantly changing stream of stimuli has been observed to evoke a spatiotemporal pattern of spike activity in ensembles of neurons in the brain. But how downstream populations discriminate one spatiotemporal pattern from another remains unclear. Surprisingly, the brain 'replays' the spatiotemporal pattern usually evoked by a stimulus in its absence. Replay is notably seen in the hippocampus, where place cells both fire sequentially over seconds as a rodent traverses a linear track and fire sequentially over tens of milliseconds—in the same sequence—after this behavior. Intriguingly, these two time scales are bridged by the NMDA plateau potential observed in a dendrite, which has an onset of a few milliseconds and a duration of several hundred milliseconds. In a compartmental model of a reconstructed layer 2/3 pyramidal cell with $GABA_B$/KIR (inwardly rectifying potassium) channels blocked, as is typically done *in vitro*, activating NMDA receptors across few microns of a basal dendrite evoked a plateau potential that spread hundreds of microns, making this branch good at detecting a coincidence but not a sequence. Unblocking KIR rescued the dendrite's ability to detect a sequence, both by shortening the distance a plateau spreads along the dendrite to about ten microns and by preventing activated AMPA receptor-channels alone from depolarizing a spine to the NMDA threshold, unless further depolarized by the spread of a nearby plateau potential, thereby advancing the plateau a few microns. Thus, spikes delivered consecutively to spines a few microns apart propel the plateau potential towards the soma. This sequence-detection mechanism robustly operated with KIR expressed either on a spine head or a dendrite shaft, as well as in a smooth dendrite with NMDA and KIR expressed on the shaft. Thus, a stretch of dendrite could detect an ensemble's spatiotemporal pattern of spike activity, provided that its afferent axons permute themselves along this stretch to activate its synapses consecutively.

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**Poster**

**PSTR007. Somatic and Dendritic Integration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR007.03/C36

**Topic:** B.06. Intrinsic Membrane Properties, Electrical Synapses, and Signal Integration

**Support:** MEXT KAKENHI Grant 21K06259
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**Title:** Subcellular local processing in the mechanosensory local non-spiking interneurons

**Authors:** K. SHIRAHATA[1], H. SHIDARA[2,3], ***H. OGAWA**[2];
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**Abstract:** Unlike spiking neurons, non-spiking neurons utilize a graded potential as a medium to encode and process sensory and motor information. The non-spiking neuron has difficulty in carrying potential changes distally because of the decay of the membrane potential in its amplitude. Instead, the non-spiking neurons possibly perform different computations from the spiking neuron by using local processing with a graded potential. Central nervous system (CNS) in invertebrates such as insects contains non-spiking neurons in the neural circuitry besides the spiking neurons. However, how and which subcellular regions in non-spiking neurons process the sensory information remains unclear. To address this issue, we examined intracellular $Ca^{2+}$ dynamics induced by the sensory stimulus in the wind-sensitive non-spiking neurons of crickets. They have a pair of mechanosensory organs called cerci to detect surrounding airflow. The directional information of airflow is processed by a local circuit within the terminal abdominal ganglion (TAG) and conveyed to the brain by ascending projection neurons, including giant interneurons (GIs). GIs have distinct selectivity to the airflow direction in the stimulus-evoked spikes. Several spiking and non-spiking local interneurons are identified within the TAG and thought to be involved in forming the GIs' directional selectivity. The previous study has reported that some of the local non-spiking interneurons (LNIs) also have directional selectivity in the graded potential changes. We measured the membrane potential and $Ca^{2+}$ responses to airflow applied from eight angles in three types of LNIs. These LNIs showed spatially heterogeneous patterns in their $Ca^{2+}$ responses. The time course of the $Ca^{2+}$ responses varied in similarity between local regions depending on their intracellular distance. In contrast, the directional selectivity in the $Ca^{2+}$ responses did not necessarily follow the intracellular distance but rather depended on the direct distance. This suggests that directional selectivity reflects synaptic input properties based on spatial maps of afferents rather than the stimulus-evoked electrical activity. In the insect CNS, the local processing by the LNIs may allow a single neuron to substitute for the functions of multiple spiking neurons, resulting in conserving the number of neurons.

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**Poster**

**PSTR007. Somatic and Dendritic Integration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR007.04/C37

**Topic:** B.06. Intrinsic Membrane Properties, Electrical Synapses, and Signal Integration

**Support:** NIMH Grant R01MH125978

**Title:** Distinct dendritic integration properties of prefrontal cortical layer 5 pyramidal cells

**Authors: *S. SCHAMILOGLU**, N. S. STONE, A. T. LIPTAK, R. L. CLARKSON, K. J. BENDER;
UCSF, San Francisco, CA

**Abstract:** In mouse prefrontal cortex (PFC), layer 5 pyramidal cells can be distinguished based on their dopamine receptor expression patterns. D1, D2, or D3 dopamine receptor-expressing (D1R+, D2R+, D3R+) pyramidal cells have distinct morphologies, intrinsic properties, and projection targets. D1R+ and D2R+ pyramidal cells map onto intratelencephalic (IT) and pyramidal tract (PT) subclasses, respectively. D1R+ IT neurons have “thin” apical dendritic shafts and apical tufts that have few branches and a narrow expansion within layer 1, whereas D2R+ PT neurons have “thick” dendritic shafts and highly arborized tufts, with extensive layer 1 lateral projections. D3R+ neurons appear to be a subclass of IT-projecting neuron that, oddly, share dendritic branching features with PT neurons, including an extensive layer 1 tuft. These anatomical differences suggest that these intermingled neuronal subclasses may integrate information differently, including how they integrate backpropagating signals from the soma with incoming synaptic input. To test this, we assessed dendritic calcium associated with backpropagating action potentials (bAPs) in D1R+, D2R+, and D3R+ pyramidal cells. We found that bursts of APs resulted in robust dendritic calcium supralinearities that were far greater than the linear sum expected from isolated APs, especially in D3R+ neurons. In D3R+ neurons, supralinearities were due to the combined activation of dendritic T- and L-type calcium channels. By contrast, D1R+ pyramidal cells exhibited modest dendritic supralinearities. Our data suggest that in these neurons, L-type calcium channels couple to large conductance calcium-activated potassium channels (BK), which limit dendritic depolarization, suppressing supralinearities. Consistent with this, blockade of BK channels resulted in an increase in supralinear linear calcium transients. Unlike in D1R+ and D3R+ pyramidal cells, bAP-evoked dendritic calcium transients in D2R+ pyramidal cells were largely linear. As with PT cells in other brain regions, we found that these neurons are enriched with hyperpolarization-activated cyclic nucleotide-gated (HCN) channels that likely limit temporal windows for bAP integration in dendrites. Consistent with this idea, we found that blocking HCN channels unmasked dendritic nonlinearities in D2R+ pyramidal cells. Taken together, our data demonstrate that PFC layer 5 pyramidal cell classes have different complements of ion channels expressed in their dendrites that result in distinct dendritic calcium properties and suggest that information flow across these three neuronal subtypes is specifically integrated and regulated.

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**Poster**

**PSTR007. Somatic and Dendritic Integration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR007.05/C38

**Topic:** B.06. Intrinsic Membrane Properties, Electrical Synapses, and Signal Integration

**Support:** Australian Government Research Training Program

**Title:** Modulation of feedback onto tuft dendrites of single neurons during closed-loop behavior

**Authors: *G. STUYT**, L. M. PALMER;
Florey Neurosci. Inst., Parkville, Australia

**Abstract:** The dendritic morphology of cortical pyramidal neurons is organised to integrate information from different input streams, however the nature of this processing in vivo remains unclear. In this study, we investigated whether compartment-specific information processing is used by dendrites during the performance of a closed-loop goal-oriented task. Using the International Brain Laboratory's open-source task, the position of a visual stimulus was determined by rotating a steering wheel. To investigate error signalling, the direction of the wheel-stimulus coupling was reversed mid-trial in a subset of trials. During task performance, two-photon calcium imaging was performed pseudo-simultaneously in distal tuft and basal dendrites of single neurons expressing Syn.GCaMP7f within the posterior parietal cortex. Here, the majority of dendritic calcium events occur simultaneously across the dendritic arbour, however, there was an increase in local tuft dendrite activity in sessions which included the reversal trials. In contrast, basal dendrites did not change their level of local activity throughout the behavior. These results indicate that modulating closed-loop behaviour can invoke differential activation of tuft dendrites compared to basal dendrites, providing further insight into the laminar-specific role of different dendritic compartments.

**Disclosures: G. Stuyt:** None. **L.M. Palmer:** None.

**Poster**

**PSTR007. Somatic and Dendritic Integration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR007.06/C39

**Topic:** B.06. Intrinsic Membrane Properties, Electrical Synapses, and Signal Integration

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**Title:** Decoding activity patterns across pyramidal cell dendritic trees during spontaneous behaviors using 3D arboreal scanning

**Authors: *T. J. YOUNTS**, A. M. VALERA, V. A. GRIFFITHS, D. COYLE, R. SILVER; Neuroscience, Physiol. and Pharmacol., Univ. Col. London, London, United Kingdom

**Abstract:** How sensorimotor information is represented across individual pyramidal cell dendritic trees in awake behaving animals remains obscure. The three key limitations are: a lack of technologies that can rapidly measure activity from entire dendritic arbors in 3D in real-time; brain motion artefacts which can severely distort signals generated by fine caliber structures like dendrites; and not having an analysis framework for exploring activity patterns that could manifest across entire dendritic trees during behavior. To overcome these challenges, we combined our recently developed nonlinear 3D acousto-optic lens two-photon microscope with real-time 3D brain motion correction along with novel $Ca^{2+}$ imaging analysis pipelines to discover how sensorimotor information is represented by patterns of dendritic activity in motor cortical layer 2/3 excitatory neurons during spontaneous naturalistic behaviors. Arboreal scanning confirmed that a strong, highly correlated, and putatively cell-wide $Ca^{2+}$ signal is the dominant activation mode in vivo. We find independent branch-specific local events are rare, and when observed, are largely accounted for by contaminating signals. Applying nonlinear dimensionality reduction techniques to the global signals, we discovered specific dendritic regions that covary with uninstructed spontaneous movements. These dendritic modulations (spread over > 20 μm compartments) were superimposed on the global signals and were dynamic across behavioral epochs including quiet-rest, locomotion, active whisker touch, and unexpected sensorimotor stimuli. Remarkably, regression analyses suggest that modulations in the activity of dendritic segments are more informative about specific behaviors than the activity at the soma for most cells. Our results indicate that L2/3 pyramidal cell dendritic activity patterns are multidimensional and represent several innate behavioral features simultaneously.

**Disclosures: T.J. Younts:** None. **A.M. Valera:** None. **V.A. Griffiths:** None. **D. Coyle:** None. **R. Silver:** None.

**Poster**

**PSTR007. Somatic and Dendritic Integration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR007.07

**Topic:** B.06. Intrinsic Membrane Properties, Electrical Synapses, and Signal Integration

**Support:** Grant-in-Aid for JSPS Fellows Grant Numbers JP22KJ1851
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**Title:** Fluorescent visualization of asymmetrically spreading excitatory synaptic potentials in hippocampal neuronal dendrites

**Authors: *M. MORITA**, R. HIGASHI, S.-Y. KAWAGUCHI;
Dept. of Biophysics, Grad. Sch. of Sci., Kyoto Univ., Kyoto, Japan

**Abstract:** Synaptic inputs are integrated spatially and temporally in the somatodendritic compartment of a neuron. Despite intensive studies for decades on synaptic integration in the somatodendritic compartments, its spatio-temporal dynamics remain obscure because of the technical limitation to obtain local potentials at multiple regions. To address this issue, we used a genetically-encoded voltage indicator, which enables us to detect membrane potential changes as fluorescence intensity changes, together with local uncaging of glutamate on cultured hippocampal neurons. Fluorescent voltage imaging using a modified version of ASAP1 (St-Pierre et al., 2014) exhibited asymmetric spreading of excitatory postsynaptic potentials (EPSPs): EPSPs amplified during propagation toward the distal end whereas attenuated toward the soma. We also found that the local amplification of EPSPs was abolished by the inhibition of TTX-resistant $Na^+$ channels and KCC2, a K-Cl cotransporter. These results suggest that low concentration of intracellular $Cl^-$ ($[Cl^-]_{in}$) in distal dendrites is important for the asymmetric spreading of EPSPs. To confirm this idea, we directly measured the resting membrane potential in a thin dendrite by the patch-clamp method. Surprisingly, the dendritic resting potential was more negative than the somatic one. In addition, the relative leak conductance became higher in a dendrite farther away from the soma. The deeper resting potential in dendrites was abolished by a KCC2 inhibitor. These data suggest that lower $[Cl^-]_{in}$ and/or higher $Cl^-$ conductance in distal dendrites than in the soma underlies deeper resting potential in dendrites. To confirm that the deeper resting potential depending on the specific $[Cl^-]_{in}$ regulation in dendrites is involved in the local augmentation of EPSP, we constructed a simple biophysical model. Simulation of the model exhibited the asymmetric augmentation of excitation depending on the TTX-resistant $Na^+$ channels and $Cl^-$ conductance accompanied with deeper dendritic resting potential. Accordingly, voltage imaging showed that the simultaneous inhibition of $Cl^-$ conductance and $Na^+$ channels strongly suppressed the local augmentation of EPSP in a distal dendrite. Taken all these results together, our findings identified a novel $Cl^-$-dependent mechanism underlying the unique asymmetric processing of the electrical signal in dendrites.

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**Poster**

**PSTR007. Somatic and Dendritic Integration**

**Location:** WCC Halls A-C

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**Topic:** B.06. Intrinsic Membrane Properties, Electrical Synapses, and Signal Integration

**Support:** NIH NINDS Grant R35 NS097185
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**Title:** Local inhibition delimits the phase resetting caused by striatal inhibition in the external globus pallidus

**Authors: *J. PENA**[1], J. A. JONES[2], C. J. WILSON[3];
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**Abstract:** Spontaneous activity of the local GABAergic synaptic network in the external globus pallidus (GPe) causes GPe neurons to fire with irregular inter-spike intervals. While the local synapses are powerful, they make up only a small portion of synapses in the GPe. Most synapses are formed by the axons of indirect pathway striatopallidal neurons (iSPNs) and axon collaterals of direct pathway striatonigral neurons (dSPNs). It is well established that both pathways are highly convergent. It is assumed that each of the individual connections in these pathways is weak. To determine the strength of iSPN-GPe and dSPN-GPe connections, we measured unitary SPN-GPe synaptic currents. We collected 10-degree tilted parasagittal mouse brain slices to preserve the striatopallidal pathways. Because SPNs are not spontaneously active in slice preparations, we used slices from Ai32 x A2A-Cre mice and Ai32 x Tac-Cre mice to allow us to induce asynchronous repetitive firing in iSPNs and dSPNs by activating channelrhodopsin (ChR2) current with blue light. We collected whole-cell voltage clamp recordings of GPe neurons' membrane current while driving SPNs expressing ChR2 to fire with low levels of illumination, localized in the striatum. Unitary inhibitory postsynaptic currents (IPSCs) from both iSPNs and dSPNs had significantly smaller amplitudes and slower kinetics than local synaptic currents. To determine the relationship between the number of striatopallidal synapses and the spiking responses of neurons in the GPe network, we injected waveforms with dynamic clamp that simulated unitary striatopallidal conductance and summated multiple waveforms to modulate the number of striatal synapses. In the absence of the local network, the input from roughly 5-10 SPNs was required to reliably reset oscillatory firing. In the presence of the local network, phase resetting caused by SPNs did not last beyond a single inter-spike interval due to the continuous de-regularization of spontaneous firing by the local network. This suggests that by de-regularizing neuronal firing, the local network limits the ability of SPNs to synchronize GPe neurons beyond a single inter-spike interval. Because GPe neurons innervate neurons in all nuclei of the basal ganglia, they may be a major source of their irregularity and active decorrelation.

**Disclosures: J. Pena:** None. **J.A. Jones:** None. **C.J. Wilson:** None.

**Poster**

**PSTR007. Somatic and Dendritic Integration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR007.09/C41

**Topic:** B.06. Intrinsic Membrane Properties, Electrical Synapses, and Signal Integration

**Support:** BBRF 304841
RO1NS128079

**Title:** Longitudinal functional investigation of dendritic integration in mouse visual cortical neurons

**Authors: L. M. ADSIT**[1], I. T. SMITH[1,2], *L. ADSIT[3];
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**Abstract:** Neurons process tens of thousands of inputs arriving at their dendritic arbor to compute reliable, tuned output in response to specific stimuli. Layer 2/3 pyramidal neurons in mouse visual cortex, with their broad dendritic arbors across superficial layers, offer a relevant model for studying the dendritic mechanisms by which a myriad of synaptic inputs are integrated to generate stimulus feature specific responses. Of these, orientation tuning is one of the fundamental computations performed by these visual cortical neurons. Using direct dendritic patch-clamp recordings in awake mice, we previously found that locally generated, NMDA receptor-dependent dendritic spikes are not only visually evoked, but also exhibit reliable orientation tuning. However, a detailed understanding of how and under what conditions the heterogeneous synaptic inputs trigger tuned dendritic spikes, and how reliably the latter instructs neuronal outputs is still lacking. Recent technical advances in two-photon calcium (2P Ca2+) imaging using genetically encoded calcium indicators, e.g., GCaMP8m, have enabled functional input mapping with dendritic spine-level resolution. This approach enables longitudinal examination of the spatial distribution of presynaptic inputs carrying various orientation tuning signals along the dendritic arbor. 2P Ca2+ imaging can also identify the site of dendritic spike generation as local dendritic hotspots of Ca2+ increase, and the generation of neuronal output observed as a global Ca2+ transient backpropagating towards distal dendrites. Here we report that while the simple linear sum of the tuning curves of individual synaptic inputs can predict the preferred orientation of the neuron, it produces broader tuning. A simple linear sum of the tuning curves of local dendritic Ca2+ hotspots, however, recapitulated both the preferred orientation and the tuning width of the neuronal output. Moreover, chronic functional imaging of the same dendrites over up to 6 months revealed several cases in which drifts in preferred orientations have been observed that were coupled with drifts in the summed tuning of dendritic spine activity. Lastly, chronic functional imaging is a powerful tool for monitoring pathological progression in neurodegenerative diseases. Performing chronic intrinsic signal optical imaging on two different strains of mouse models of tauopathy (rTg4510 and PS19), we have identified specific visual cortical areas of vulnerability including the primary visual cortex (V1) and medial higher visual areas (HVAs). Focusing on these visual areas, we will discuss how dendritic integration is affected as the pathology progresses.

**Disclosures:** **L.M. Adsit:** None. **I.T. Smith:** None. **L. Adsit:** None.

**Poster**

**PSTR007. Somatic and Dendritic Integration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR007.10/C42

**Topic:** B.06. Intrinsic Membrane Properties, Electrical Synapses, and Signal Integration

**Title:** Hidden HCN channels in cortical L2/3 pyramidal neurons are critical for sensory information processing

**Authors: *V. J. OLAH**, M. J. ROWAN;
Emory Univ. Sch. of Med., Atlanta, GA

**Abstract:** Neocortical layer 2/3 (L2/3) pyramidal cells are a major component of the canonical cortical circuit. Although these cells are the most numerous cortical pyramidal cell type, restricted access to their fine dendritic protrusions has limited our understanding of the somato-dendritic conductances governing the activity of these cells. Hyperpolarization-activated nonselective cation (HCN) channels are known to play an essential physiological role in the more well-characterized (e.g., L5) pyramidal cell types. In L5 pyramidal neurons, HCN channels regulate resting membrane potential and are crucial for the temporal normalization of synaptic events arriving at spatially mismatched locations. In contrast, L2/3 pyramidal cells are widely regarded as lacking this conductance due to the absence of the characteristic “sag” potential. Here we report that L2/3 pyramidal cells express functionally relevant HCN channels throughout the cortex. Importantly, HCN channels strongly constrained neuronal AP firing by altering the resting membrane potential and input resistance of L2/3 cells. In L5 cells, HCN channels strongly regulate distal synaptic events due to their enrichment within distal apical dendrites of this neuron type. In contrast, we found that only proximal synaptic events were altered in L2/3 cells after pharmacological HCN blockade. Thus, this unique L2/3 HCN distribution may preferentially regulate information arriving from bottom-up synaptic pathways, as opposed to top-down information in L5 cells. We also found that direct HCN modulation through serotonergic receptor (5-$HT_7$R) activation significantly altered AP firing in L2/3 neurons. Finally, we confirmed that these channels have behaviorally relevant functionality in the adult brain for maintaining accurate visual processing in V1 cortex. Together our results demonstrate that L2/3 pyramidal cells not only express dendritic HCN channels but also employ these conductances in a previously unobserved manner.

**Disclosures:** **V.J. Olah:** None. **M.J. Rowan:** None.

**Poster**

**PSTR007. Somatic and Dendritic Integration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR007.11/C43

**Topic:** B.06. Intrinsic Membrane Properties, Electrical Synapses, and Signal Integration

**Support:** ERC Starting Grant #678250
NARSAD young investigator grant #27653

**Title:** Interneuron-specific dendritic computations in the neocortex

**Authors: *N. REBOLA**[1], A. MORABITO[1], Y. ZERLAUT[1], D. DHANASOBHON[1], E. BERTHAUX[1], G. MONERON[2], L. CATHALA[1], A. BACCI[1], D. DIGREGORIO[3], J. LOURENCO[1];
[1]Paris Brain Institute-ICM, Paris, France; [2]Inst. Pasteur, Paris, France; [3]CU Sch. of Medicine, Anschutz Sch. of Med., Aurora, CO

**Abstract:** Neurons receive the majority of their excitatory synaptic inputs on dendritic trees, which can differ in shape, size, and density of active conductances. This diversity can differentially affect dendritic integration and hence neuronal computations. While the role of dendrites in computations performed by excitatory neurons has been substantially investigated, much less is known about the influence of dendritic integration in GABAergic interneurons (INs). This is particularly true in the neocortex where interneurons are particularly diverse. In here we used a multidisciplinary approach to characterize the dendritic integration properties of parvalbumin (PV)-positive and somatostatin (SST)-positive INs in the mouse sensory cortex. Using two-photon glutamate uncaging (2PGLU) we observed that PV-INs display mostly sublinear subthreshold input-output relationships, while SST-IN dendrites integrate quasi-synchronous inputs supralinearly in a NMDA-dependent manner. We subsequently analyzed synaptic distributions on those two different populations of INs using STED imaging of immunolabelled PSD-95 puncta (proxy for glutamatergic synapses) as well as a publicly-available EM dataset (MICrONS dataset). Surprisingly, estimates of synapse distributions revealed that PV- and SST-INs use different strategies to distribute synaptic inputs along their dendrites. In SST-INs, linear synapse density is relatively constant along single dendritic branches. In contrast, in PV-INs, proximal dendrites have linear synapse density that is 2-3 times higher than in SST-INs that progressively decreases with distance from soma. Interestingly 2PGLU revealed that such asymmetric synapse distributions are accompanied by synaptic integration gradients. In PV-INs proximal dendritic segments integrate inputs in a predominantly linear fashion, whereas distal dendritic segments exhibit predominantly sublinear integration. Initial results from numerical simulations suggest that the sharp decrease in synapse density along the somatodendritic axis of PV cells reduces sublinear processing in their distal dendrites during normal cortical function. We are presently using visual stimulation and two-photon imaging to test the link between sensory integration and dendritic properties in the primary visual cortex of awake mice. Notably, we are testing the impact of NMDARs in SST-INs in shaping the spatial selectivity of neuronal responses. In conclusion, our data demonstrate that IN-specific dendritic integration properties further contribute to the already diverse functional differences between $PV^+$-INs and $SST^+$-INs in neocortical microcircuits.

**Disclosures:** **N. Rebola:** None. **A. Morabito:** None. **Y. zerlaut:** None. **D. Dhanasobhon:** None. **E. Berthaux:** None. **G. Moneron:** None. **L. Cathala:** None. **A. Bacci:** None. **D. DiGregorio:** None. **J. Lourenco:** None.

**Poster**

**PSTR007. Somatic and Dendritic Integration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR007.12/C44

**Topic:** B.06. Intrinsic Membrane Properties, Electrical Synapses, and Signal Integration

**Support:** NIH Grant R01NS113079

**Title:** Using Soma-targeted Optogenetic Inhibition To Probe Dendritic Computation

**Authors: *C. WU**[1], J. VOIGTS[2], T. PHAM[1], M. T. HARNETT[1];
[1]Brain and Cognitive Sci., MIT, Cambridge, MA; [2]HHMI's Janelia Res. Campus, Ashburn, VA

**Abstract:** Morphologically elaborate dendritic trees endow cortical pyramidal neurons with the ability to differentially integrate multiple streams of information. Although prior calcium imaging studies have shown that active dendritic processes can represent task-relevant features in behaving animals, it remains unclear how such dendritic activity is related to somatic spiking due to interference from backpropagating action potentials (bAPs). To study the relationship between somatic and dendritic activity, we employed soma-targeted optogenetic inhibition to suppress bAPs generation during multi-plane two-photon *in vivo* GCaMP imaging of apical dendrites. Experiments were performed in the mouse retrosplenial cortex during navigation in a virtual reality paradigm. We observed widespread and highly correlated somato-dendritic activity in cortical layer 5 pyramidal neurons under control conditions, as has been reported previously. However, during optogenetic inhibition of bAPs generation, many independent local GCaMP events in distal apical tuft branches were revealed. Ongoing experiments are focused on characterizing the visual inputs and behavioral correlates of these events compared to somatic bAPs. Our approach provides a new avenue for investigating how dynamic compartmental computations in dendrites contribute to neuronal tuning and cortical circuit processing during behavior.

**Disclosures:** **C. Wu:** None. **J. Voigts:** None. **T. Pham:** None. **M.T. Harnett:** None.

**Poster**

**PSTR008. Epilepsy: Networks Changes and Modifications**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR008.01/C45

**Topic:** B.08. Epilepsy

**Support:** NIH R01 NS100019
University of Illinois RB21053

**Title:** Striatal-enriched protein tyrosine phosphatase regulates seizure susceptibility, hippocampal excitability, and hyperpolarization-activated cyclic nucleotide-gated channels.

**Authors: *H. A. NOBLET**[1,2], E. KIM[2,3], J. M. WALTERS[1,2], A. BAJAJ[2], H. CHUNG[1,2,3,4]; [1]Neurosci., Univ. of Illinois Urbana-Champaign Neurosci. Grad. Program, Urbana, IL; [2]Mol. and Integrative Physiol., [3]Beckman Inst., [4]Inst. of Genomic Biol., Univ. of Illinois Urbana-Champaign, Urbana, IL

**Abstract:** Temporal lobe epilepsy (TLE) is a neurological disorder characterized by focal seizures originating from the hippocampus, hippocampal sclerosis, and cognitive dysfunction. Many TLE patients are unresponsive to current epilepsy treatments, highlighting the need to understand the mechanisms underlying hippocampal hyperexcitability that drive the seizure onset. In the hippocampus and cortex, STriatal-Enriched protein tyrosine Phosphatase (STEP61) is membrane-bound and negatively regulate s excitatory synaptic transmission by inducing dephosphorylation and internalization of two major glutamatergic receptors including N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Recently, we have reported that the STEP inhibitor, TC-2153, decreased the severity of kainate (KA)-induced seizures and activity of acute hippocampal slices compared to DMSO vehicle control. Further, TC-2153 treatment of cultured hippocampal neurons decreased their excitability and ¬the hyperpolarization-activated current (Ih¬), highlighting a potential novel regulation of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels by STEP61. To test this hypothesis, we first demonstrated that STEP knock-out (KO) mice displayed reduced excitability of hippocampal CA1 neurons and similar severity of KA-induced seizures between TC-2153 and DMSO treatment, indicating that anti-seizure action of TC-2153 is STEP-specific. To investigate if STEP61 regulates HCN channels, we next performed surface biotinylation in Chinese hamster ovary (CHOhm1) cells transfected with HCN2 and wild-type (WT) STEP61, or a catalytically inactive mutant of STEP61 [C/S]. Although HCN2 colocalizes with STEP61 WT and [C/S] , co-expression of STEP61 WT nor STEP61 [C/S] did not alter total expression of HCN2 compared to empty vector control. Interestingly, co-transfection of STEP61 [C/S] significantly increased HCN2 surface level compared to STEP61 WT. Together, these results suggest that TC-2153 reduces seizure susceptibility in a STEP-specific manner and that STEP61 regulates surface expression of HCN2. We are currently testing whether STEP61 affects voltage-dependent activation, current density, and tyrosine phosphorylation of HCN2 channels.

**Disclosures: H.A. Noblet:** None. **E. Kim:** None. **J.M. Walters:** None. **A. Bajaj:** None. **H. Chung:** None.

**Poster**

**PSTR008. Epilepsy: Networks Changes and Modifications**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR008.02/C46

**Topic:** B.08. Epilepsy

**Title:** Elevated SUR1-TRPM4 Expression Due to Chronic Seizures Contributes to Epileptogenesis

**Authors: *M. MOYER**[1], S. IVANOVA[2], J. OWOTADE[2], M. BACHANI[2], V. GERZANICH[3], A. KSENDZOVSKY[2], M. J. SIMARD[2];
[2]Neurosurg., [1]Univ. of Maryland, Baltimore, MD; [3]Neurosurg., Univ. of Maryland Sch. of Med., Baltimore, MD

**Abstract:** **Rationale**: Current anti-seizure medications are insufficient for managing seizures in epilepsy patients, as one third of patients are resistant to current anti-convulsants. One promising disease-specific target for reducing seizures is SUR1-TRPM4, a sodium conducting ion channel minimally expressed in healthy brain that upregulates *de novo* after status epilepticus and other seizure-related pathologies like stroke. SUR1-TRPM4 upregulation has been successfully targeted to reduce stroke pathology through preclinical studies and clinical trials. Here we investigated whether SUR1-TRPM4 upregulation contributes to chronic seizure susceptibility in epilepsy. **Methods**: SUR1-TRPM4 expression was examined by immunohistochemistry (IHC) in epilepsy patient resected brain tissues electrographically sorted as normal or epileptic, as well as in brains from mice undergoing pentylenetetrazol (PTZ) kindling compared to sham controls. To assess SUR1-TRPM4 contribution to chronic seizures, the effects of TRPM4 inhibition were studied *in vivo* and *in vitro*. An adapted PTZ kindling model was used to assess differences in chronic seizure threshold between global TRPM4 knock-out (KO) and littermate wildtype controls (WT). PTZ doses were started at 15mg/kg and escalated by 5mg/kg every 3 doses until seizures were seen in either group, after which that dose (25mg/kg) was used. To assess the mechanism that SUR1-TRPM4 expression promotes seizures through neuron hyperexcitability, rat cortical cultures were recorded with microelectrode array (MEA), treated with low $Mg^{2+}$ or control aCSF daily, and co-treated with either TRPM4 inhibitor CBA or vehicle. **Results**: Compared to controls, SUR1-TRPM4 expression was increased within epileptic tissues resected from patients ($p<0.05$, paired t-test) and in PTZ kindled brains ($p<0.05$, unpaired t-test). Furthermore, TRPM4 KO significantly attenuates ($p<0.05$, logistical regression analysis) the development of seizures induced by PTZ kindling and pharmacological inhibition of SUR1-TRPM4 *in vitro* reduces ($p<0.01$, 2-way ANOVA) neuronal population hyperactivity induced by low $Mg^{2+}$. **Conclusions**: These findings suggest that SUR1-TRPM4 is overexpressed within seizure-specific tissue from epilepsy patients. Furthermore, this channel is upregulated in mouse PTZ kindling and TRPM4 KO in this model reduces seizure susceptibility. *In vitro* data suggest SUR1-TRPM4 contributes to seizure development through neuronal population hyperexcitability. Overall, this work suggests SUR1-TRPM4 is a clinically relevant biomarker and potential therapeutic target to manage seizures in epilepsy patients.

**Disclosures:** **M. Moyer:** None. **S. Ivanova:** None. **J. Owotade:** None. **M. Bachani:** None. **V. Gerzanich:** None. **A. Ksendzovsky:** None. **M.J. Simard:** None.

**Poster**

**PSTR008. Epilepsy: Networks Changes and Modifications**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR008.03/C47

**Topic:** B.08. Epilepsy

**Support:** NS29709

**Title:** Unraveling the Complex Inheritance and Social Behavior Abnormalities in Childhood Absence Epilepsy: Insights from a Digenic Mouse Model

**Authors: *Q. MIAO**, J. OKOH, M. COSTA-MATTIOLI, J. NOEBELS;
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**Abstract:** Epilepsy is a prevalent neurological disorder characterized by recurrent seizures, affecting millions of individuals worldwide. Among various forms of epilepsy, childhood absence epilepsy (CAE) is particularly common in pediatric patients and is believed to have a strong genetic component. Despite its familial clustering, CAE does not follow a simple Mendelian inheritance pattern, suggesting a complex polygenic nature. In addition to seizure activity, cognitive impairments and social behavior abnormalities are frequently observed in neurodevelopmental disorders, including CAE. However, the behavioral aspects of developmental and epileptic encephalopathy (DEE) and their response to anti-seizure medications are not well understood.

In this study, we investigated the combined effects of heterozygous mutations in two human CAE and/or ASD (autism spectrum disorder)-associated genes, CACNA1A and CACNG2, which encode the α-subunit of P/Q-type calcium channels ($Ca_v2.1$) and a transmembrane AMPA receptor regulatory protein (TARP) named stargazin, respectively. Using a digenic mouse model ($DiG^{stg+1A}$) carrying both mutations, we demonstrated that these genetic alterations led to the development of CAE and alterations in social novelty preference. Furthermore, we evaluated the efficacy of ethosuximide, a commonly prescribed anti-CAE medication, in this mouse model. While ethosuximide successfully suppressed absence seizures, it failed to restore social novelty preference in the $DiG^{stg+1A}$ mice. This observation aligns with clinical findings that neurocognitive impairments persist in CAE patients, even with successful seizure control under first-line anti-seizure medications like ethosuximide.

Our findings present the first digenic animal model that replicates the complex inheritance patterns observed in human CAE. The $DiG^{stg+1A}$ mice exhibit altered social behavior that is resistant to ethosuximide treatment, mirroring the condition observed in human patients. This study provides valuable insights into the intricate heredity of CAE and lays the foundation for the development of novel therapeutic interventions to address this disorder in the future.

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**Poster**

**PSTR008. Epilepsy: Networks Changes and Modifications**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR008.04/C48

**Topic:** B.08. Epilepsy

**Title:** Progressive maladaptive homeostatic plasticity resulting from sustained activity blockade

**Authors: *D. L. WISE**[1], S. B. NELSON[2], S. VAN HOOSER[3];
[1]Neurosci., Brandeis Univ., Somerville, MA; [2]Dept Biol MS#008, [3]Brandeis Univ., Waltham, MA

**Abstract:** Forebrain neurons deprived of activity become hyperactive when activity is restored. Rebound activity has been linked to spontaneous seizures in vivo following blockade with the sodium channel blocker tetrodotoxin (TTX). Here we measured the time course of rebound activity and contributing circuit mechanisms using calcium imaging, synaptic staining and whole cell patch clamp of organotypic slice cultures of mouse neocortex. Calcium imaging revealed hypersynchronous activity increasing in intensity with longer periods of deprivation. While activity partially recovered three days after slices were released from five days of deprivation, they were less able to recover after ten days. However, even after the longer period of deprivation, activity patterns eventually returned to baseline levels. Pharmacological blockade of NMDA receptors indicated that elevated rebound activity did not require Hebbian plasticity evoked during synchronous firing. Single neuron recordings revealed that input resistance roughly doubled with a concomitant increase in intrinsic excitability. Synaptic imaging of pre- and postsynaptic proteins revealed dramatic changes in the number of presumptive synapses with larger effect on presumptive inhibitory than excitatory synapses. Presumptive excitatory synapses colocalizing PSD-95 and Bassoon declined by 39% and 56% following five days and ten days of deprivation, but presumptive inhibitory synapses colocalizing gephyrin and VGAT declined by 55% and 73% at these time points. More modest changes in pre- and postsynaptic puncta size also occurred. The results suggest that with prolonged deprivation, a progressive reduction in synapse number is accompanied by a shift in the balance between excitation and inhibition and increased cellular excitability.

**Disclosures: D.L. Wise:** None. **S.B. Nelson:** None. **S. Van Hooser:** None.

**Poster**

**PSTR008. Epilepsy: Networks Changes and Modifications**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR008.05/C49

**Topic:** B.08. Epilepsy

**Support:** NIH R01NS126594

**Title:** Spike wave seizure generation in childhood absence epilepsy

**Authors: *E. DULKO**, S. KILIANSKI, I. G. LESMANA, A. CARNS, S. HE, M. P. BEENHAKKER;
Pharmacol., Univ. of Virginia, Charlottesville, VA

**Abstract:** The spike-wave seizure (SWS) is the hallmark of Childhood Absence Epilepsy (CAE), a disease that affects up to 8 per 100,000 children under 15 years of age. Currently available anti-seizure medications reduce seizure occurrence but are associated with unacceptable freedom from treatment failure rates (~50%) due to intolerable side effects. Understanding the mechanisms of SWS generation is a necessary step for developing better, targeted treatments. Prior research suggests that SWSs are driven by hypersynchronous neural circuits of the cortex and thalamus. However, beyond this general conclusion, many significant questions remain. For example, which structures actively contribute to the generation of a seizure ("actively driving"), and which ones are only passively active during a seizure ("passively following")? Importantly, only structures that are "actively driving" seizures are reasonable targets for treatment strategies. To resolve this question, we recorded single-unit activity in awake head-fixed epileptic mice to resolve the contribution of all thalamic nuclei to SWS generation. The activities of single neurons were aligned to the SWS onset, revealed by simultaneously recorded cortical electrocortigram electrodes. Preliminary findings (n=7) indicate that most thalamic nuclei are recruited during the SWS and fire sparsely but synchronously during each cycle of the SWS. The results of this study – a single-neuron resolution activity map during the SWS - is an essential first step for the development of novel therapeutic strategies for a common childhood form of epilepsy associated with unacceptable failure rates.

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**Poster**

**PSTR008. Epilepsy: Networks Changes and Modifications**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR008.06/C50

**Topic:** B.08. Epilepsy

**Title:** Bilateral hippocampal patterned EEG activity proceeding optogenetic induced mesial temporal lobe seizures

**Authors: *S. CHEN**, F. C. TESCAROLLO, H. SUN;
Rutgers, The State Univ. of New Jersey, Piscataway, NJ

**Abstract:** Mesial temporal lobe epilepsy (mTLE) is a prevalent type of epilepsy with a high rate of drug resistance and surgery relapse. The ictogenesis of mTLE is not well understood. A better understanding of how mTLE seizures begin may offer new therapeutic opportunities.
We modeled mTLE seizures with optogenetic stimulation to the hippocampus. In mice, we transduced ChR2 in putative glutamatergic neurons unilaterally in CA1 of the hippocampus. A

fiber cannula was implanted at the site of ChR2 transduction for optical stimulation, and electrodes were implanted bilaterally in the CA1 and DG of the hippocampus to simultaneously monitor the EEG activity. We demonstrate that focal to bilateral tonic-clonic seizure can be induced in awake-behaving mice by 10Hz optical activation of unilateral CA1 glutamatergic neurons.
At first, optical stimulation of the ChR2-expressing neurons evoked an immediate EEG activity measured near the stimulation site. EEG activity at the corresponding contralateral hippocampus was observed with approximately 5ms delay, validating bilateral hippocampal connectivity. To a continual stimulation, a stereotypical secondary discharge emerged in both the ipsilateral and contralateral EEG. This secondary discharge was found 20-50ms delayed from each stimulation pulse. The secondary discharge led into the seizure onset and thus denotes a critical transition from a reactive, stimulation-driven neural response to a self-sustaining seizure. We demonstrate that the secondary discharge may have been initiated in the ipsilateral DG, then amplified by the contralateral hippocampus. Overall, EEG activity appeared to alternate between the ipsilateral and contralateral hippocampus, approximately 90° out-of-phase. We believe this is the result of the neural signal rebounding between ipsilateral and contralateral hippocampus through its bilateral re-entrant structure. It is likely that the continual optically stimulation propelled the derived contralateral response to the magnitude that it activated a re-entrant response on the ipsilateral side, and this triggered the secondary discharges. Further reinforced by the external optical stimulation, both ipsilateral and contralateral secondary discharge intensified and led to a seizure.

**Disclosures: S. Chen:** None. **F.C. Tescarollo:** None. **H. Sun:** None.

**Poster**

**PSTR008. Epilepsy: Networks Changes and Modifications**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR008.07/C51

**Topic:** B.08. Epilepsy

**Title:** Mapping bilateral seizure spread by excitatory and inhibitory calcium imaging and electrophysiology

**Authors: *J. E. NIEMEYER**[1], F. ZHAN[1], P. LUO[2], H. MA[1], T. H. SCHWARTZ[1];
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**Abstract:** The prevalence of epilepsy is about 1% of the US population and nearly 1 in 3 epilepsy patients fails to respond adequately to anti-epileptic drugs. Development of new therapeutic options depends on an understanding of how seizures start and spread through the brain. Two main features of seizure propagation are the excitation/inhibition balance across the brain, and the specific brain regions involved in individual seizures to form a seizure network. To examine excitation and inhibition balance across the cortex, we selected a bilateral neocortical brain network consisting of somatosensory (S1) and frontal cortex (M2). We applied

widefield calcium imaging across the dorsal cortex during awake focal 4-Aminopyridine (2.5 mM) seizures in mice to study how seizures initiate and spread, imaging Thy1+ excitatory neurons and PV+ interneurons with simultaneous electrophysiology. We found that, prior to seizure onset, both cell types show activity increase at the focus, though there was no significant timing difference between these cell types. After seizure onset, seizures either propagated contiguously, spreading from the 4-AP focus, or by first propagating through axonal connections to ipsilateral M2. After this, some seizures then propagated to the opposite hemisphere. When this occurred, our imaging revealed that bilateral propagation always occurred earlier in frontal cortex than other more posterior regions. Contralateral S1, despite direct callosal connection with the seizure focus, was recruited significantly later than contralateral M2. This finding suggests that bilateral seizure propagation may depend on the dynamics of cross-callosal projections: we hypothesize that callosal projections from S1 may serve to inhibit contralateral S1, while callosal projections from M2 may preferentially excite contralateral M2. Regardless of the mechanism, our data suggests that specific choke points may exist within seizure networks and provides a potential target for cell-type-specific or surgical intervention to prevent bilateral seizure spread.

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**Poster**

**PSTR008. Epilepsy: Networks Changes and Modifications**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR008.08/C52

**Topic:** B.08. Epilepsy

**Support:** Mitacs Accelerate Fellowship
Phramongkutklao College of Medicine
Doctoral Completion Award
Wildcat Graduate Scholarship
Friends of Faces
New York University School of Medicine

**Title:** Neural Network Dynamics in Amygdala Kindled Seizures

**Authors: *A. R. PEIMANI**[1,2], W. SANGPHOSUK[2], P. L. CARLEN[1,2];
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**Abstract:** In this study, we explored the progression of seizures kindled from the basolateral amygdala (BLA) using an amygdala rapid kindling rat model Responses were measure in to the ipsilateral parietal cortex (PC), fastigial nucleus (FN), and the brainstem reticular formation (RF) and nucleus tractus solitarius (NTS), Adult male Wistar rats were surgically implanted with bipolar electrodes, enabling real-time, high-resolution local field potential (LFP) recordings pre-, and postictally. Utilizing a combination of graph neural network (GNN) and Granger Causality

(GC) analyses, we transformed raw LFP data into discernible patterns of functional connectivity. We observed a strengthened GC connectivity from the BLA to NTS, FN, PC, and RF during seizure progression associated with once daily stimulation of the BLA over 3 weeks. Interestingly, post-kindling stages presented a shift in seizure centrality from the BLA to the ipsilateral PC, which demonstrated stronger connections to NTS, RF, and FN, while BLA connectivity appeared to diminish. This distinct pattern of activity flow and synchronization suggested a coherent progression of seizures from supratentorial regions to subcortical and cardiorespiratory hubs within the brainstem. Statistical analyses further supported these findings, showing significant increases in synchronization and coherence metrics during seizure propagation compared to baseline states. Remarkably, these synchronization patterns correlated with the severity of Racine scored seizures. Brainstem seizure activity correlated with the degree of respiratory dysfunction, establishing a quantitative link between neural activity and systemic physiological impacts. By elucidating the complex neural network dynamics of kindled seizures, our study provides a perspective on seizure propagation into the brainstem and the associated seizure semiology and physiological consequences.

**Disclosures:** **A.R. Peimani:** None. **W. Sangphosuk:** None. **P.L. Carlen:** None.

**Poster**

**PSTR008. Epilepsy: Networks Changes and Modifications**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR008.09/C53

**Topic:** B.08. Epilepsy

**Support:** NIH K99NS121274
NIH P30 DA048742
American Epilepsy Society Postdoctoral Fellowship
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a University of Minnesota McKnight Land-Grant Professorship award

**Title:** Chronic, spontaneous hippocampal seizures evoke widespread alterations in cerebellar activity and network dynamics in a mouse model of temporal lobe epilepsy

**Authors: *M. STRENG**, B. W. KOTTKE, E. M. WASSERMAN, L. ZECKER, L. LUONG, T. J. EBNER, E. KROOK-MAGNUSON;
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**Abstract:** Despite not being traditionally associated with epilepsy or seizures, the cerebellum has emerged as a potentially critical node in seizure networks. Chronic epilepsy is associated with cerebellar alterations including disrupted functional and structural connectivity, volume, and perfusion. During seizures themselves, alterations in cerebellar blood flow and phase locking of single cell activity occur, but it is unclear how these alterations influence ongoing cerebellar

processing. It is critical to understand exactly how seizures and chronic epilepsy influence cerebellar dynamics, as cerebellar deficits can coincide with cognitive impairments and can even predict sudden unexplained death in epilepsy (SUDEP).To address these major questions, we recently developed a novel method for chronic mesoscale recordings of the of the cerebellar cortex in head fixed, behaving mice using cerebellar windows. Using PcP2-GCaMP6s mice, the activity of Purkinje cells, the primary output neurons of the cerebellar cortex, is recorded across lobules IV-VII of both vermis, simplex, and Crus I regions of the cerebellar cortex. Combined with simultaneous hippocampal LFP recordings in mice that had previously received unilateral intrahippocampal kainic acid injections, our approach allows for the quantification of Purkinje cell modulation during chronic, spontaneous hippocampal electrographic seizures. We find that hippocampal electrographic seizures evoke widespread alterations in Purkinje cell activity throughout the dorsal cerebellar cortex. Importantly, these seizures lack any overt motor symptoms, indicating that cerebellar modulation cannot be attributed to pure changes in motor output. In addition to being engaged by the seizures themselves, changes in cerebellar activity precede hippocampal seizures, with dramatic reductions in synchrony observed between cerebellar networks during preictal periods. Together, these results indicate that hippocampal seizures can profoundly influence cerebellar activity, and suggest that alterations in cerebellar dynamics might potentially serve as a predictor of seizure onset in temporal lobe epilepsy.

**Disclosures:** **M. Streng:** None. **B.W. Kottke:** None. **E.M. Wasserman:** None. **L. Zecker:** None. **L. Luong:** None. **T.J. Ebner:** None. **E. Krook-Magnuson:** None.

**Poster**

**PSTR008. Epilepsy: Networks Changes and Modifications**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR008.10/C54

**Topic:** B.08. Epilepsy

**Support:** NIH NINDS K22NS104230

**Title:** Mc4rs facilitate fear extinction learning and acth-driven neuroprotection after early life seizures

**Authors: *M. KHALIFE**[1,2], P. JASINSKI[2], K. ABED RABBO[3], M. OUARDOUZ[2], M. MAHONEY[4], R. C. SCOTT[1,2,5], A. E. HERNAN[1,2];
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**Abstract:** Pediatric epilepsy is a common neurological disorder characterized by recurrent unprovoked seizures, but often associated with severe cognitive impairments and psychiatric comorbidities that are detrimental to the patient’s quality of life. Current treatment approaches do

not address the disease associated cognitive and psychiatric comorbidities. Rodents with a history of early life seizures (ELS) have significant deficits in spatial learning and memory, sociability, attention, and fear extinction learning. We have shown that exogenously administered adrenocorticotropic hormone (ACTH), a hormone in the hypothalamic-pituitary-adrenal (HPA) axis, is effective at preventing learning impairments in fear extinction and anxiety phenotype in light/dark box after ELS. The objective of this study is to investigate the mechanism behind the cognitive improvement and learning impairment prevention of ACTH after ELS. Here we show that the cognitive improvement is dependent on melanocortin 4 receptors (mc4r), neuropeptide receptors agonized by ACTH that are expressed on neurons and glia in the brain. To investigate the mechanism behind the improvement, both male and female wildtype and mc4r knockout mice were distributed into three groups: control, ELS with no treatment and ELS with ACTH treatment. Mice experience seizures between p10 and p14 followed by *in vivo* single unit recording implantation in the prefrontal cortex (PFC) at p45. *In vivo* single unit recordings performed at baseline (n=24 wildtype and n=18 mc4r knockout p50 mice) and during a fear extinction task (n=18 wildtype and n=13 mc4r knockout p50 mice) reveal that ELS and ACTH treatment are associated with long-term alterations in PFC neuronal firing modulation. These results suggest that ACTH treatment improves cognitive outcome after ELS through a mechanism that bypasses the systemic effects of cortisol release and potentially normalizes local PFC networks independently from altering seizure parameters. Taken together, these data elucidate the mechanism behind the improvement in ELS outcome with ACTH treatment and suggest that MC4R agonists may be a novel therapeutic strategy for improving outcome in pediatric epilepsy.

**Disclosures:** **M. Khalife:** None. **P. Jasinski:** None. **K. Abed Rabbo:** None. **M. Ouardouz:** None. **M. Mahoney:** None. **R.C. Scott:** None. **A.E. Hernan:** None.

**Poster**

**PSTR008. Epilepsy: Networks Changes and Modifications**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR008.11/C55

**Topic:** B.08. Epilepsy

**Support:** NIH/NINDS grant #R01-NS071785-14

**Title:** Cortical network dysfunction in a C1qa knockout mouse model of epilepsy

**Authors: *J. RIGHES MARAFIGA**, T. VU, S. C. BARABAN;
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**Abstract:** In the United States, nearly 400,000 children suffer from developmental epileptic encephalopathies characterized by intellectual disability, behavioral comorbidities, higher rates of mortality and increasing drug resistance risk with age. Although involvement of inhibitory circuits in modulating abnormal neuronal networks and seizure development is known, our

understanding of GABAergic interneurons in epileptic encephalopathies remains limited. Here, we used a C1qa KO mouse model of epilepsy that exhibits clinically relevant electrophysiological (EEG) and behavioral features of refractory childhood epilepsies, particularly Lennox-Gastaut syndrome (LGS). We investigated EEG abnormalities, inhibitory neuronal network changes and behavioral phenotypes. Data was obtained from juvenile adult C1qa KO mice and aged-matched controls between 60-80 days postnatal (n = 22 WT, 30 C1qa KO). EEG signals were acquired using a tethered head-mounted video-EEG monitoring system and analyzed offline using SireniaScore software (Pinnacle Technologies). In an additional cohort of mice, we performed two independent behavioral assays: open field test and dark light preference test, to assess anxiety-like behaviors and general locomotor activity. Immunofluorescence labeling for somatostatin (SST)-expressing interneurons, DAPI and c-Fos was performed in the same cohort of mice. Measurement of interneuron numbers was performed in somatosensory cortex layers (I-VI). Cortical excitatory and inhibitory synaptic transmission was also evaluated using *in vitro* electrophysiology. Here, we present four major findings: C1qa KO mice showed (1) a prominent bi-hemispheric irregular spike and slow wave activity pattern, (2) a transient period of hyperactivity during open field testing, and decreased time spent in the light compartment while in a dark/light box, both associated with anxiety-like behaviors, (3) decreased number of SST interneurons and c-Fos positive cells in layer 6 of somatosensory cortex, (4) increased amplitude and frequency of spontaneous EPSC in deep layers of somatosensory cortex. These results uncover cortical network abnormalities and behavioral phenotypes in a C1qa KO mouse model of epilepsy.

**Disclosures: J. Righes Marafiga:** None. **T. Vu:** None. **S.C. Baraban:** None.

**Poster**

**PSTR008. Epilepsy: Networks Changes and Modifications**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR008.12/C56

**Topic:** B.08. Epilepsy

**Support:** NIH RO1 NS040337
NIH RO1 NS044370
UVA Brain Institute

**Title:** Neuronal plasticity leads to seizure-induced apnea

**Authors: *A. BRODOVSKAYA**[1], N. ADOTEVI[1], J. KAPUR[2];
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**Abstract:** Repeated generalized tonic-clonic seizures (GTCSs) are the single most significant risk factor for sudden unexpected death in epilepsy (SUDEP). Others have demonstrated that animals with ion channel mutations causing epilepsy have postictal apnea. We reported last year

that repeated PTZ-induced seizures gradually lead to fatal postictal apnea, related to the plasticity of the GluA1 subunit of AMPA receptors. We tested whether similar mechanisms operate in the kindling model of temporal lobe epilepsy. We induced repeated GTCSs using the hippocampal kindling model. We generated global knockout (K.O.) mice of AMPA receptor subunit GluA1 and compared EEG, breathing, and heartbeat in GluA1 K.O. and W.T. littermates. Kindled mice underwent hypoxia (10% $O_2$) and hypercarbia (5% $CO_2$) gas challenge every other day before kindling from naïve to fully kindled states to determine if there are any gas sensitivity changes before apnea development. Breathing frequency and variability were recorded in plethysmography chambers. Next, we kindled activity reporter TRAP2 mice to label and map neuronal circuits active during postictal apnea. Because the amygdala has been shown to be involved in apnea, we injected Cre-dependent AAV9 GFP virus in the amygdala of TRAP2 mice that express Cre only in the activated neurons. Injection of 4-hydroxytamoxifen in these mice after postictal apnea allowed us to trace only activated anatomic projections from the amygdala through the brainstem during apnea. We used immunohistochemistry and NeuroInfo software to create a 3D brainstem reconstruction map of activated brainstem nuclei during postictal apnea. We found that repeated hippocampal kindling-induced GTCSs also led to fatal postictal apnea. Mice without GluA1 subunit of AMPA receptors neither attained nor sustained GTCSs compared to W.T. littermates. 60% of GluA1 K.O. mice remained unkindled despite stimulation, their seizure threshold was higher (GluA1 K.O.: 157.10 ± 37.65 μA, n = 10 mice; W.T.: 64.00 ± 14.70 μA, n = 10 mice; Mann Whitney test, $p = 0.022$), seizure severity lower ($p < 0.05$), seizure duration shorter, and none of them died compared to W.T.s. The experiments mapping neuronal circuits active during hippocampal GTCSs-induced apnea in TRAP2 mice and sensitivity to hypoxia and hypercarbia during kindling are ongoing. We propose that neuronal plasticity leads to seizure-induced apnea.

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**Poster**

**PSTR008. Epilepsy: Networks Changes and Modifications**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR008.13/C57

**Topic:** B.08. Epilepsy

**Support:** Floyd and Mary Schwall Fellowship for Medically-Related Research
NSF NRT Neuroengineering Fellowship (NeuralStorm)

**Title:** Using Dynamic Network Connectivity States for Seizure Prediction

**Authors: *A. N. MOGHBEL**[1], K. MOXON[2], S. C. TOPRANI[3];
[1]Neurosci. Grad. Program, Univ. Of California Davis, Davis, CA; [2]Biomed. Engin., Univ. of California Davis, Davis, CA; [3]Clin. Neurology, Neurosurg., Univ. of California, Davis, Davis, CA

**Abstract:** Rationale: Although epilepsy patients spend minimal time experiencing seizures, significant physical injury and psychological distress is associated with the unpredictability of these transient, debilitating events. Despite four decades of EEG-based predictive modeling of neural features such as LFP band power changes and single neuron firing rates, the transitions between baseline, pre-seizure, and seizure brain states remain unclear and unpredictable.
Methods: In contrast, our approach uniquely models time-varying epileptic network connectivity across seizure development to reveal predictable, distinct connectivity states across seizure development. We analyze intracranial EEG (iEEG) recordings from three patients with drug-resistant epilepsy, tracking coherence between electrode contacts. High-dimensional connectivity data is projected into low-dimensional latent space using principal component analysis. Data points are grouped into stages of seizure development by temporal proximity to seizure, and clustering of points within and between stages is quantified.
Results: Our results in three subjects demonstrate that within subjects and across multiple seizures, grouping data points based on temporal proximity to seizure explains significantly more variance in connectivity state than can be attributed to the temporal dependence inherent to time-series data (p < 0.0001). This suggests that network connectivity evolves through predictable, distinct connectivity states across seizure development. Specifically, we find that changes in high gamma band coherence (70-200 Hz) drive the majority of variance and that theta (4-8 Hz) and alpha (8-12 Hz) coherence optimally separate pre-seizure from baseline states.
Conclusion: Our results characterize a distinct pre-seizure connectivity state, which is separable from both baseline and seizure states. Identification of this state could provide a dynamic target for seizure prediction. Our initial analyses temporally defined stages of seizure development and assessed whether these temporal stages exhibited significant differences in network connectivity. Future work will challenge the assumption of our initial temporal grouping, finding optimal borders of distinct connectivity states in time relative to seizure.

**Disclosures:** **A.N. Moghbel:** None. **K. Moxon:** None. **S.C. Toprani:** None.

**Poster**

**PSTR008. Epilepsy: Networks Changes and Modifications**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR008.14/C58

**Topic:** B.08. Epilepsy

**Title:** Forecasting seizures using evoked response features in tetanus toxin induced epilepsy in rats

**Authors: *W.-C. CHANG**[1], J. LIN[2], A. LAI[3], M. J. COOK[4], W. C. STACEY[5,6];
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**Abstract:** Seizures are common and greatly impact patients' lives because they are abrupt and difficult to predict, thus developing biomarkers that can reliably signal seizures' approaches is of great interest. Prior work on seizure prediction has focused on monitoring passive changes in EEG. An alternate strategy is to monitor the response to perturbations, which is based upon critical slowing from dynamic systems theory. In this study, we forecast seizure retrospectively in a rat temporal lobe epilepsy model using pre-seizure features associated with critical slowing. Tetanus toxin (TeNT, 25 ng/ul) was infused into the left hippocampal CA3 of six male Sprague Dawley rats; three control rats were injected with vehicle alone. Four EEG screw electrodes were implanted anterior or posterior to the ipsilateral and contralateral hippocampi respectively. From the second day after TeNT injections, intermittent electrical stimuli (pulse incidence, 0.3 Hz; pulse length and amplitude: 0.5 & 0.5 ms, biphasic 1.2 mA; 100 pulses in a train, and the inter-train interval = 5 min) were delivered through the two EEG screws flanking the ipsilateral hippocampus as a consistent source of perturbations. The first electrographic seizures presented in the first two weeks after TeNT injections, and the rats remained epileptic for 8 weeks. Recording and stimuli lasted over 2 months after injections. We characterized several response features (curvature, point of deflection, spectral band power [1-64 Hz], etc) that were successful at suggesting that seizure risk was rising in the 0-30 minutes prior to seizures. For each subject, we built a custom seizure forecasting algorithm through the comparison of features between interictal periods and pre-seizure periods. We tested how this method could be implemented in real-time preparation for an online evaluation of seizure risk in the same model of epilepsy.

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**Poster**

**PSTR008. Epilepsy: Networks Changes and Modifications**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR008.15/C59

**Topic:** B.08. Epilepsy

**Support:** NIH/NINDS Grant R21NS116937

**Title:** The O-GlcNAc transferase is associated with the ten-eleven translocation enzyme to control DNA hydroxymethylation in the epileptic hippocampus

**Authors: *A. M. SCHREIBER**, R. BAHABRY, F. D. LUBIN;
Neurobio., Univ. of Alabama, Birmingham, Birmingham, AL

**Abstract:** Background: Temporal lobe epilepsy (TLE) is one of the most common types of epilepsy, with seizures originating from the hippocampus and is associated with aberrant DNA hydroxymethylation and glucose hypometabolism. Approximately 5% of glucose feeds into the Hexosamine Biosynthetic Pathway (HBP), which is a precursor to the glycosylation pathway, generating the sugar nucleotide UDP-N-acetyl-glucosamine (UDP-GlcNAc) substrate. The *O*-

GlcNAc Transferase (OGT) and *O*-GlcNAcase (OGA) catalyze the addition and removal of the *O*-GlcNAc moiety at serine and threonine residues, respectively. In the present study, we investigated whether OGT recruits Ten-Eleven Translocation (TET) proteins, like TET1, to facilitate the conversion of 5-methylcytosine (5-mC) to 5-hydroxymethylcytosine (5-hmC) at gene regions associated with chronic epilepsy. We hypothesize that altered TLE associated glucose metabolism contributes to abnormal *O*-GlcNAc signaling to TET1 DNA hydroxymethylation mechanisms in the epileptic hippocampus. Methods: Male Sprague Dawley rats were injected with saline or 10mg/kg of kainic acid (KA) to induce Status Epilepticus (SE). Six weeks following SE induction, the hippocampus was sub-dissected out and tissue processed for TET1 and OGT interactions in nuclear protein extraction. TET1, OGT and *O*-GlcNAc levels were detected by western blotting. The physical interaction of TET1-OGT was assessed by co-immunoprecipitation (co-IP). *O*-GlcNAcylation of TET1 was determined by succinylated wheat germ agglutinin (sWGA) assay. Results: Co-immunoprecipitation analysis revealed that endogenous TET1 complexed with OGT in the hippocampus. Specifically, we found a significant increase in the ratio of OGT binding to TET1 in the epileptic hippocampus compared to non-epileptic controls. Furthermore, we observed a significant reduction in TET1 *O*-GlcNAcylation levels. Conclusions: Together, these findings indicate an increased association between OGT and TET1 proteins in the hippocampus of epileptic rats compared to non-epileptic controls. To our knowledge, this study is the first to demonstrate an endogenous interaction of OGT-TET1 in the epileptic hippocampus suggesting a possible dysregulation in the following: 1) glucose metabolism, 2) expression/activity of OGT/OGA, 3) cellular stress response or 4) other epigenetic mechanism influencing the expression of genes involved in HBP. Our future work will focus on elucidating the observed alterations in TET1-OGT interaction and TET1 *O*-GlcNAcylation gene regions in the epileptic hippocampus.

**Disclosures: A.M. Schreiber:** None. **R. Bahabry:** None. **F.D. Lubin:** None.

**Poster**

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**Topic:** B.08. Epilepsy

**Support:** NIH Grant 1R37NS115439

**Title:** Preventing Adult Neurophysiological Dysfunction and Restoring Hippocampal Network Activity through Early Treatment with the GluA2-lacking AMPAR Blocker IEM-1460 following Early-life Seizures

**Authors: *B. XING**, X. LI, E. LANCASTER, S. DUTKO, A. BARBOUR, D. TALOS, F. JENSEN;
Univ. of Pennsylvania, Philadelphia, PA

**Abstract:** Early life seizures (ELS) can have long-term consequences on cognitive function, leading to persistent cognitive deficits and intellectual disability. We have previously shown that ELS elevate neuronal excitability and increase the expression of GluA2-lacking AMPARs. In addition, ELS can block critical period cortical plasticity, and cause synaptic long-term potentiation (LTP) deficits in hippocampal CA1. Since the re-appearance of GluA2-lacking AMPARs play a critical role in aberrant plasticity in the hippocampus after ELS, we investigated whether a single seizure episode affects specific populations within the hippocampus, and whether early intervention through antagonism of GluA2-lacking AMPARs can prevent long-lasting dysfunction in neuroplasticity at adulthood. Using an activity-dependent genetic labeling transgenic mouse model (FosTRAP;Ai14**)**, we permanently labeled the ELS-activated neuronal population by pairing kainic acid with 4-OHT injections at postnatal day (P)10. The ELS-activated neurons, tagged by tdTomato (tdT+), were assessed at P28-35. A subset of mice received an intraperitoneal injection of IEM-1460, a GluA2-lacking AMPAR antagonist, at 5 mg/kg, 1 hr post-seizures and 3 more injections every 12 hrs. We found a robust population of tdT+ neurons in CA1 (93.5 ± 8.9%), and these neurons showed increased inward rectification consistent with synaptic insertion of GluA2-lacking AMPARs compared with surrounding tdT- neurons and saline control mice (rectification index, tdT+: 3.58 vs tdT-: 1.84 vs saline: 1.64, $p < 0.05$, one-way ANOVA), as well as impaired LTP (Kruskal-Willis ANOVA, $p < 0.05$; Dunn's post-test, Sal vs tdT+ cells, $p< 0.05$, and tdT- vs tdT+, $p < 0.05$), and diminished long-term depression (LTD; one-way ANOVA, $p < 0.001$; Tukey's post-test, Sal vs tdT+ cells, $p < 0.01$, and tdT- vs tdT+ cells, $p < 0.001$). However, the surrounding tdT- showed robust LTP and LTD, comparable to the saline controls. Importantly, we found that early treatment with IEM-1460 at P10 could prevent the GluA2-lacking AMPARs accumulation onto synapses of tdT+ neurons at P28-P35 (ELS+IEM vs ELS+Veh, Mann Whitney test, $p < 0.05$), and at the same time, rescue LTP (one-way ANOVA followed by Tukey's test, ELS+IEM vs ELS+Veh, $p < 0.001$) and LTD deficits (one-way ANOVA followed by Tukey's test, ELS+IEM vs ELS+Veh, $p < 0.05$) in the CA1 neurons. In summary, this study emphasizes the significant role played by GluA2-lacking AMPARs in a particular subset of neurons that are impacted by ELS, ultimately leading to dysfunction within the hippocampal network and emphasizes the need to prioritize preventive measures in individuals affected by ELS.

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**Poster**

**PSTR008. Epilepsy: Networks Changes and Modifications**

**Location:** WCC Halls A-C

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**Topic:** B.08. Epilepsy

**Support:** Epilepsy Research UK (ERUK) Project Grant

**Title:** Neural correlate of reduced respiratory chemosensitivity during chronic epilepsy

**Authors: *A. M. BHANDARE**, N. E. DALE;
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**Abstract:** While central autonomic cardiorespiratory dysfunction underlies sudden unexpected death in epilepsy (SUDEP), the specific neural mechanisms that lead to SUDEP remain to be determined. Here we took an advantage of single cell neuronal Ca2+ imaging and intrahippocampal kainic acid (KA)-induced chronic epilepsy in 8-10 weeks old male C57BL/6 mice to investigate progressive changes in key cardiovascular and respiratory brainstem circuits during chronic epilepsy. Experiments were performed in accordance with the European Commission Directive 2010/63/EU and the UK Home Office Scientific Procedures Act (1986). Mice were randomly elected from the cage and assigned to injection group (respiratory retrotrapezoid nucleus (RTN) n=9, cardiovascular rostral ventrolateral medullary (RVLM) n=9 or control n=6). Following induction of status epilepticus (SE), we observed that the adaptive ventilatory responses to hypercapnia were reduced in mice with chronic epilepsy for 5 weeks post-SE with its partial recovery at week 7. These changes were paralleled by post-SE alterations in the chemosensory responses of neurons in the RTN. Neurons that displayed adapting responses to hypercapnia were less prevalent and exhibited smaller responses over weeks 3-5, whereas neurons that displayed graded responses to hypercapnia became more prevalent by week 7. Over the same period, chemosensory responses of the presympathetic RVLM neurons showed no change. Mice with chronic epilepsy showed enhanced sensitivity to seizures, which invade the RTN and possibly put the chemosensory circuits at further risk of impairment. Our findings establish a dysfunctional breathing phenotype with its RTN neuronal correlate in mice with chronic epilepsy and suggests a potential functional non-invasive biomarker test, based on respiratory chemosensitivity, to identify people with epilepsy at risk of SUDEP.

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**Poster**

**PSTR008. Epilepsy: Networks Changes and Modifications**

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**Topic:** B.08. Epilepsy

**Support:** NIH Grant 5R35NS116852

**Title:** Brain extracellular matrix alters local anion concentrations and responses to injury

**Authors: *K. P. NORMOYLE**[1], V. I. DZHALA[2], K. P. LILLIS[4], K. EGAWA[5], J. GLYKYS[6], K. J. STALEY[3];
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Charlestown, MA; [5]Med., Hokkaido Univ., Sapparo, Japan; [6]Univ. of Iowa, Univ. of Iowa, Iowa City, IA

**Abstract:** The reversal potential of $GABA_A$ receptors ($E_{GABA}$) is dependent upon the chloride concentrations on both sides of the neuronal membrane. We recently discovered that the extracellular chloride concentration is non-uniform and half the chloride in bulk cerebrospinal fluid. We also observed that removal of polyanionic glycosaminoglycans (GAGs) from the extracellular space, mimicking injury-induced metalloprotease (MMP) activation, results in a shift toward higher local extracellular chloride concentrations. We used 2-photon Fluorescence Lifetime Imaging (FLIM) of a custom chloride-sensitive fluorophore constrained to the extracellular space by conjugation with 10 kilodalton dextran in acute and organotypic cultures of hippocampal slices. We used slice injury as well as 2-photon photolysis of single neurons within organotypic slices to model acute brain injuries. Intraneuronal chloride was measured with the ratiometric reporter Super Chlomeleon. Having discovered that the extracellular chloride ($[Cl^-]_o$) between neurons both *in vitro* and *in vivo* is only about half that of bulk CSF chloride, and that digestion of a prominent sulfated GAGs in the brain (chondroitin sulfate) leads to release of these anionic moieties and a shift to higher chloride concentrations, we next asked what would happen to $[Cl^-]_o$ when the sulfated moieties of the matrix are freed by endogenous MMPs after brain injury. We found a strong dependence of $[Cl^-]_o$ vs distance from injury, with Cl concentration increasing to the ACSF levels near the injured surface of acute slices or proximity to photolysed neurons in organotypic slices. These changes in $[Cl^-]_o$ should also alter the neuronal intracellular chloride via the activity of the high-velocity equilibrative membrane chloride transporters. We compared $[Cl^-]_o$ and intracellular chloride ($[Cl^-]_i$) in each of these models, and confirmed results *in vivo* using cortical window implantation of adolescent mice. Finally, the release of sulfates and subsequent changes to $[Cl^-]_{o/i}$ should be inhibited by MMP antagonists. We confirmed that broad-spectrum inhibition using the zinc chelator ZX-1 or the more specific MMP-2/9 inhibitor SB3CT also reduced $[Cl^-]_{o/i}$ and neuronal volume after injury. These changes were evident at the cut surface of acute brain slices and in proximity to photolysed neurons. In conclusion, $[Cl^-]_o$ is partially displaced by sulfates in the extracellular matrix. Damage to the extracellular matrix following brain injury alters the distribution of chloride in both the extra- and intracellular spaces. These findings have immediate implications for the treatment of cytotoxic edema and seizures after acute brain injury.

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**Poster**

**PSTR009. Animal Models of Epilepsy: Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR009.01/C63

**Topic:** B.08. Epilepsy

**Support:** NIH Grant R15S088776

**Title:** Seizures, Impaired Motor Performance, and Altered Markers of Vitamin D Signaling and Metabolism in the Cerebellum are Uncorrected by High Dose Vitamin D in NS-Pten KO Mice

**Authors: *D. NARVAIZ**[1], D. SANTANA-COELHO[1], G. O'NEILL[1], D. TRAN[2], J. PILCHER[1], A. SMELLEY[1], K. J. BLANDIN[1], J. N. LUGO[1];
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**Abstract:** Genetic mutations that cause hyperactive mTOR signaling in the cerebellum lead to disrupted cerebellar growth, debilitating motor impairments, and may contribute to the development of epilepsy. mTOR inhibitors can reduce seizures and prevent behavioral impairments but are associated with serious side effects. Thus, a critical need for better therapies to treat individuals with hyperactive mTOR induced motor impairments and epilepsy remains. Vitamin D has been shown to suppress mTOR signaling and abate seizure severity. However, it has not been determined if vitamin D can ameliorate the development of motor impairments and epilepsy induced by hyperactive mTOR signaling. Here, we determine the effects of high dose vitamin D on cerebellar growth, mTOR signaling, and markers of vitamin D signaling and metabolism in a mouse model of hyperactive mTOR induced epilepsy and ataxia. Male and female neuronal subset specific *Pten* knockout (KO) and wildtype (WT) mice were provided either a diet supplemented with 20,000 IU/Kg of vitamin D3 or a standard mouse chow containing 1,500 IU/Kg of vitamin D3 at 4-weeks-old. At 6 weeks, mice underwent testing for motor performance in the sticker removal, spontaneous activity in a cylinder and rotarod tests. Motor seizures were recorded during weeks 9 and 10. The cerebellum was weighed and then analyzed for alterations to vitamin D and mTOR signaling. KO mice exhibited baseline impairments in expression of the vitamin D receptor, *Vdr*, and in *Cyp24a1*, a key enzyme in vitamin D catabolism. KO mice showed increased phosphorylation of AKT, S6 (S240/244) and S6 (S235/236) in the cerebellum, and were found to have increased cerebellar weight, motor seizures, and impaired motor performance in all behavioral tasks. S6 (S235/236) was marginally suppressed by high dose vitamin D. However, no other measures were corrected by high dose vitamin D and instead led to increased cerebellar growth in WT mice and impaired rotarod performance in both KO and WT mice. In addition to confirming motor impairments and describing motor seizures in the NS-PTEN KO mice, we also provide evidence that KO mice may exhibit intrinsic impairments in vitamin D signaling. Although high dose vitamin D at this dose had no effect on mTOR signaling, led to increased cerebellar growth in WT mice, and impaired rotarod performance in all mice, these data may suggest that this dose lies on the far side of a U-shaped curve of effects, leading to impairments. Future work determining a dose response curve of vitamin D on neuronal mTOR signaling are expressly needed.

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**Poster**

**PSTR009. Animal Models of Epilepsy: Mechanisms**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR009.02/D1

**Topic:** B.08. Epilepsy

**Support:** NS125884
NS127428

**Title:** Deletion of the mitochondrial $Ca^{2+}$ uniporter (MCU) produces marked resistance to seizures in mice

**Authors: *T. NGUYEN**[1], G. C. WALTERS[2], J. RYSTED[2], Z. LIN[2], B. S. PURNELL[3], S. STRACK[2], G. F. BUCHANAN[4], Y. M. USACHEV[2];
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**Abstract:** Epilepsy is a neurological disorder characterized by the presence of chronic seizures. It is a major public health concern because of the economic burden and medical issues it brings to patients with epilepsy and society. While epileptic seizures can be controlled through pharmaceutical therapies, approximately 30% of patients with epilepsy can develop refractory epilepsy, which does not respond to medication. Refractory epilepsy is associated with a higher risk of sudden unexpected death in epilepsy (SUDEP), the leading cause of mortality in epilepsy patients. Thus, there is a critical need to develop targeted therapeutics for patients with refractory epilepsy. Here, we examined the role of mitochondrial $Ca^{2+}$ transport in regulating neural hyperexcitability and seizures. The mitochondrial calcium uniporter (MCU) is a highly conserved pore-forming subunit of the MCU complex that mediates $Ca^{2+}$ uptake into the mitochondrial matrix. Deletion of MCU resulted in impaired $Ca^{2+}$ uptake into mitochondria in neurons, inhibited mitochondrial $Ca^{2+}$ dysregulation and excitotoxicity in brain mitochondria. We found that MCU deletion prevents the induction of epileptiform activity by chemo-convulsant agents in vitro. In a model of maximal electroshock-induced (MES) seizures, global MCU deletion in mice (CD1 background) produced strong anticonvulsant effects. Furthermore, neuron-specific deletion of MCU (C57BL/6 background) significantly increased the threshold of seizure induction, and markedly reduced severity of seizures. When examining the specific roles of MCU in excitatory and inhibitory neurons, we found that MCU deletion in inhibitory, but not excitatory, neurons was sufficient to produce a significant anticonvulsant effect. Extensive behavioral testing did not detect any significant changes in sensory, motor, or cognitive functions in MCU KO mice. These results indicate that MCU could represent an attractive novel molecular target for the development of new anticonvulsant therapeutics.

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**Poster**

**PSTR009. Animal Models of Epilepsy: Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR009.03/D2

**Topic:** B.08. Epilepsy

**Support:** NIH/NINDS Grant NS115049

**Title:** Interleukin-1 Type 1 Receptor (IL-1R1) is implicated in emergence and severity of seizures in a transgenic mouse model of progressive, generalized tonic/clonic epilepsy.

**Authors: T. DILLON**, A. KHAN, A. TRAN, *C. ISGOR;
Biomed. Sci., Florida Atlantic Univ. Charles E Schmidt Col. of Med., Boca Raton, FL

**Abstract:** Interleukin-1 (IL-1) is an inflammatory cytokine with neuromodulatory properties in the CNS. IL-1 expression is increased in both epilepsy patients and animal models of epilepsy, and exogenous application of IL-1 has proconvulsive properties. Here we test if interfering with intracellular signaling cascades initiated with IL-1 binding to its type 1 receptor (IL-1R1) will suppress epileptogenesis and/or alter the severity of the seizures in epileptic mice. We use a transgenic mouse model of adult-onset, spontaneous epilepsy. The mice overexpress brain derived neurotrophic factor (BDNF) in the forebrain under the CAM kinase II alpha promoter (TgBDNF). TgBDNF mice develop generalized tonic/clonic seizures (GTCSs) at ~3 months of age which worsen with each episode. Seizures are elicited via tail lifts and cage agitation only. GTCSs become more severe as indicated by increased duration of postictal cortical activity suppression associated with loss of posture/consciousness. In more advanced stages, the mice expire following a long period of postictal generalized EEG suppression (PGES) resulting in cardiorespiratory arrest. Here we crossed TgBDNF mouse strain with a strain that lacks IL-1R1 globally to assess the epileptogenesis of the bigenic homozygote offspring. We included IL-1R1 deficient homozygotes as negative controls and TgBDNF mice with normal expression of IL-1R1 as positive controls. We surgically implanted subdural cortical electrodes on the mice skulls prior to the first seizure episode (3- channel EEG system, Pinnacle Technology, KS) to record seizure EEG across four months of seizure assessment weekly. The recordings targeted time periods of onset, moderate and severe phases of GTCSs progressively. With successive GTCSs, positive control TgBDNF mice showed progressively heightened severity of seizures as evidenced by increased duration of PGES associated with loss of posture/consciousness, and death risk. In contrast, in TgBDNF mice with deficient IL-1R1$^{-/-}$ the onset of GTCSs were either delayed or were completely abolished. Moreover, when the TgBDNF mice with IL-1R1 deficiency developed GTCSs, the PGES duration was brief, with rapid recovery to baseline and did not show dynamic worsening associated with successive GTCS events that is normally seen in the TgBDNF strain. Negative controls did not develop any EEG epileptiform activity. These findings implicate a role for IL-1R1 signaling in an animal model of adult-onset GTCSs that progressively increase in severity with clinical relevance for sudden unexpected death following generalized seizures.

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**Poster**

**PSTR009. Animal Models of Epilepsy: Mechanisms**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR009.04/D3

**Topic:** B.08. Epilepsy

**Support:** DOD W15QKN-16-9-1002

**Title:** An isoflurane-anesthetized rat preparation for evaluating effects of OP-based acetylcholinesterase inhibitors and reactivators in the rat basolateral amygdala

**Authors: *J. THINSCHMIDT**[1], J. D. TALTON[2], S. W. HARDEN[1], C. J. FRAZIER[1]; [1]Univ. of Florida, Gainesville, FL; [2]Alchem Inc., Alachua, FL

**Abstract:** Organophosphate (OP) nerve agents produce dangerous and sometimes fatal effects involving perturbation of AChE in the central and peripheral nervous systems. Developing more effective countermeasures is crucial, as standard therapeutics are often ineffective due to limited penetration of the blood-brain barrier (BBB). We recently established a rat brain slice assay to evaluate the efficacy of AChE reactivators in regions involved in seizure generation after acute exposure to OP-based AChE inhibitors (Thinschmidt et al. 2022). The assay detected hyperexcitation induced by the AChE inhibitor 4-nitrophenyl isopropyl methylphosphonate (NIMP) in voltage-clamped basolateral amygdala (BLA) neurons, which was dependent on activation of M1 muscarinic acetylcholine receptors and was reversed by treating slices with the AChE reactivator HI-6. In an extension of this work, we established an anesthetized (isoflurane) rat model that enables recordings of sustained OP-induced respiratory depression and electrographic seizure-like activity in the BLA following intravenous delivery of NIMP (0.5 - 0.75mg/kg). Field recordings in the BLA and measures of respiratory function were used to monitor reversal of NIMP-induced seizure-like activity and respiratory depression following intravenous administration of a non-selective muscarinic antagonist, and a reduction of respiratory depression following intravenous administration of an AChE reactivator against low doses of NIMP (0.375mg/kg). However, we found an AChE reactivator could not reverse seizure-like activity when administered alone using intravenous delivery at doses up to 80mg/kg. These findings suggest that this assay could be a valuable tool for assessing the efficacy of novel counteracting agents against OP poisoning. The results align with the compounds' ability to cross the BBB, as AChE reactivators generally exhibit limited permeability, while atropine readily crosses the BBB. Comparing in vitro and in vivo data may indicate the ability to cross the BBB in compounds effective in reversing OP effects both in brain slices and after systemic administration. Conversely, compounds effective in brain slices but ineffective systemically may indicate an inability to cross the BBB. While our in vitro model uses exogenous ACh, this assay enables monitoring of hyperexcitation produced by endogenous cholinergic activity. It includes intact cholinergic projection pathways and allows monitoring of respiratory rate, providing a comprehensive assessment of OP-induced effects.

**Disclosures: J. Thinschmidt:** None. **J.D. Talton:** Other; Owner and CEO of Alchem Inc. **S.W. Harden:** None. **C.J. Frazier:** None.

**Poster**

**PSTR009. Animal Models of Epilepsy: Mechanisms**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR009.05/D4

**Topic:** B.08. Epilepsy

**Support:** NS111389
NS126418

**Title:** Changes in Tanycytes in Preclinical Epilepsy: Implications for Metabolic Homeostasis

**Authors: *P. RAFIEI**[1], H. MIAN[2], S. IYER[2], S. DRAVES[3], M. DUNLAY[5], T. A. SIMEONE[4], K. A. SIMEONE[6];
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**Abstract: Changes in Tanycytes in Preclinical Epilepsy: Implications for MetabolicHomeostasis**Seizures can induce injury, ectopic neurogenesis, and metabolic dysfunction andsevere seizures can propagate to the hypothalamus. The hypothalamus has regulatoryinfluence over important functions including sleeping, cardiorespiration, emotion andeating. Tanycytes are cells in the hypothalamus that surround the third ventricle andfacilitate communication between the CSF and local hypothalamic regions to ensuremetabolic homeostasis. Here, we tested the hypothesis that seizures dysregulatetanycytes in preclinical epilepsy using Kv1.1 knockout mice, a preclinical model ofspontaneous recurrent seizures. We used fluorescent immunohistochemistry andrandom systematic stereology to determine changes along the dorsal-ventral aspect(alpha and beta tanycytes, respectively) and along the anterior-posterior aspect of thethird ventricle. In preclinical epilepsy, we found a reduction of (i) GFAP, a marker forall tanycytes ($p$ <0.01); (ii), GLUT1, a functional marker of glucose transport($p$ <0.01); (iii) and BLBP, a functional marker for brain lipid binding ($p$ <0.01). Thesechanges occurred in specific subtypes along the dorsal-ventral and anterior-posterioraspects of the third ventricle. The reduction indicates either a reduction in the numberof tanycytes, or an increase in the neurogenic and proliferative properties of tanycytes.However, we found no difference in DCX (doublecortin, a marker of neurogenesisand proliferation), suggesting the reduction may be due to cell death. These changesoccurred in specific regions in preclinical epilepsy, indicating the changes inmetabolic homeostasis will influence local hypothalamic nuclei and their respectivefunctions.

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**Poster**

**PSTR009. Animal Models of Epilepsy: Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR009.06/D5

**Topic:** B.08. Epilepsy

**Support:** NIH RO1 NS111122

**Title:** Gabaergic signaling and epilepsy in novel mouse models of vitamin B6 deficiency

**Authors: *B. WANG**[1], W. CHI[2], X. ZHUANG[1];
[1]Univ. of Chicago, Chicago, IL; [2]Neurol., Northwestern Univ., Chicago, IL

**Abstract:** Development of long-term non-invasive epilepsy treatments are crucial as more than one third of patients do not respond to anti-epilepsy drugs (AEDs) or develop resistance over time. One class of drug-resistant epilepsies occurs in humans with mutations in the pyridoxal-5-phosphate oxidase (*PNPO*) gene. The PNPO protein is involved in conversion of dietary vitamin B6 into pyridoxal-5-phosphate (PLP), a coenzyme critical for synthesis of neurotransmitters GABA and dopamine, among others. Severe and rare loss-of-function *PNPO* mutations can directly cause neonatal epilepsy. In addition, *PNPO* was identified as 1 of 16 most significant epilepsy risk genes, suggesting that some common *PNPO* variants cannot cause epilepsy by themselves, but may contribute to epilepsy susceptibility through interactions with other genes or the environment (i.e., diet). Despite this interesting spectrum of functional consequences, the mechanism of *PNPO* contribution to epilepsy has not been well-studied. We generated knock-in fly (PNAS 119:e2115524119; Hum Mol Genet. 28:3126) and mouse models containing the human epilepsy D33V and R116Q *PNPO* point mutations (56% and 16% enzymatic loss-of-function, respectively). Self-crosses of D33V/+ and R116Q/+ show normal Mendelian ratios at birth. Homozygous D33V mutants exhibit spontaneous seizures at P15 and require supplementary PLP feeding for survival. Heterozygotes of both mutant alleles are healthy and fertile but exhibit increased seizure susceptibility upon flurothyl inhalation, increased hyperactivity, and impaired spatial learning and memory, especially carriers of the more severe D33V mutation. These behavioral deficits are correlated with reduced PNPO expression in both knock-in mice and altered PNPO localization in R116Q knock-in mice. Continuous wireless iEEG also revealed a prevalence for low frequency cortical activity in heterozygous D33V knock-in mice, suggesting increased seizure susceptibility at baseline. *In-vivo* photometry after viral expression of an extracellular GABA sensor suggested reduced GABA release in mutants. We aim to use these mice to understand the contribution of *PNPO*-mediated GABA deficiency and gene-diet interactions in seizure development, and to develop treatments for this type of drug-resistant epilepsy.

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**Poster**

**PSTR009. Animal Models of Epilepsy: Mechanisms**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR009.07/D6

**Topic:** B.08. Epilepsy

**Title:** Eeg phenotyping as a loop translation tool to address the pathophysiology of gaba-a-signaling-associated brain disorders

**Authors: *V. DUVEAU**[1], A. EVRARD[2], B. MANDÉ-NIEDERGANG[3], C. ROUCARD[4], Y. ROCHE[5];
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**Abstract:** Developing neurotherapeutics requires appropriate tools to improve the translatability of preclinical data into clinical outcomes. Recent progresses in “omics” research have enabled to better understand disease pathophysiology and identified different subgroups of patients within a same brain disorder. The future of medicine relies on the ability to deliver a more tailored and personalized medicine to patients. Moving back to preclinical trials, finding the most translational models that are relevant to these disease subtypes or pathways count among the most promising avenues to make CNS drug development more effective. In this work, we took advantage of quantitative electroencephalography (qEEG) to characterize one humanized transgenic mouse line carrying GABA pathway mutation observed in patients with rare diseases. EEG recordings were conducted on freely-moving animals (WT, heterozygote and homozygote) from adult males and females equipped with appropriate electrodes, and quantified offline (epileptic events and full spectral analysis). We first evaluated the occurrence of epileptic events in this mouse line. Heterozygote mice showed intermittent epileptic activity, whereas homozygote mice showed a near continuous epileptic activity, this phenotype being present in both males and females. The power spectra from the three genotypes differed prominently over a frequency range from ~4 to ~30 Hz. In particular in the frontal cortex, the spectral power was graded between genotypes, with lower values in WT animals (both genders) to higher values in homozygote animals (both genders). The maximum power in most genotypes was in the theta range, between 4 and 8 Hz. This frequency range was quantified in all animals. A significant effect of genotype was found ($F_{2,34} = 75.98$, $p < 0.0001$) with no effect of the sex ($F_{1,34} = 0.0001617$, $p = 0.9899$). Paired comparisons indicated that both male and female homozygote had significantly higher power in the theta range, compared to their WT counterparts. The difference between heterozygote and WT was not significant. Conclusion: EEG sensitivity allows dynamic characterization and differentiation of translational humanized models of brain disorders. The combination of translational preclinical models and EEG represents the next step in translating preclinical trials into clinical practice, opening the era of precision medicine for patients.

**Disclosures:** **V. Duveau:** A. Employment/Salary (full or part-time); SynapCell SAS. **A. Evrard:** A. Employment/Salary (full or part-time); SynapCell SAS. **B. Mandé-Niedergang:** A. Employment/Salary (full or part-time); SynapCell SAS. **C. Roucard:** A. Employment/Salary (full or part-time); SynapCell SAS. **Y. Roche:** A. Employment/Salary (full or part-time); SynapCell SAS.

**Poster**

**PSTR009. Animal Models of Epilepsy: Mechanisms**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR009.08/D7

**Topic:** B.08. Epilepsy

**Support:** GR5270815

**Title:** A functional analysis of ASH1L in the mouse model

**Authors: *K. M. CORTEZ**[1], H. HIGASHIMORI[2], C. PAPENDORP[2], J. LIU[2];
[1]Mol. biology, cell biology, and biochemistry, Brown Universitiy, Providence, RI; [2]Neurosci., Brown Univ., Providence, RI

**Abstract:** A mutation in the ASH1L gene is known to be a major risk factor for epilepsy and autism. 1/3 to 2/3 of all children with an ASH1L mutation has epilepsy. Further, epilepsy and autism have a 30% comorbidity. Very little is known about how ASH1L causes these seizures. The ASH1L or "Absent, Small, or Homeotic 1-Like" gene is a histone methyltransferase thought to methylate lysine 36 (H3K36) and lysine 4 (H3K4) on histone 3, which are essential for transcriptional initiation and elongation. ASH1L's absence is thought to enable polycomb repressive complex-2 (PRC2) to bind to DNA and disrupt expression of genes essential to normal development. ASH1L haploinsufficiency in our gene-trap mouse model mirrors the mutations we see in humans, who are observed to always be haploinsufficient for ASH1L when carrying the mutation. An EEG conducted on the whole brain showed most seizures in $ASH1L^{gt/+}$ mice in the C57BL/6J background are isolated in the hippocampus, though some generalized seizures were present. In this study, we asked if intrinsic properties of neurons in the hippocampus of $ASH1L^{gt/+}$ mice can elucidate the mechanism of seizure activity observed in the EEG. Whole-cell patch-clamp electrophysiology was done on pyramidal neurons in the CA1 of coronal brain slices of WT and $ASH1L^{gt/+}$ C57BL/6J mice; allowing us to directly measure the membrane potential and the amount of current passing across the cell membrane. Preliminary results showed intrinsic excitability in the hippocampus is increased in $ASH1L^{gt/+}$ mice compared to wildtype mice, suggesting a functional difference in ASH1L haploinsufficient neurons during development. We find that $ASH1L^{gt/+}$ mice require significantly less injected current to fire the first action potential, at approximately 45 picoamps versus 55 picoamps in wildtype mice, possibly due to premature firing relative to neurons in wildtype mice. We also find that action potentials fire more frequently in $ASH1L^{gt/+}$ mice than wildtype mice in the same window of time. Concurrently, we saw that $ASH1L^{gt/+}$ mice have a normal membrane resistance, resting membrane potential, and cell capacitance for their age. These results describe a neuronal phenotype within the hippocampus of ASH1L haploinsufficient mice. We have also shown that the ASH1L gene trap mouse model recapitulates epilepsy in humans very well. Lastly, the trends in the intrinsic properties of the CA1 neurons raise the question of whether development in the hippocampus is disrupted.

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**Poster**

**PSTR009. Animal Models of Epilepsy: Mechanisms**

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**Program #/Poster #:** PSTR009.09/D8

**Topic:** B.08. Epilepsy

**Support:** NIH Grant R01 NS124855
NIH Grant R01 NS093992

**Title:** Timp3-mediated control of pro-epileptogenic aberrant neurogenesis

**Authors: *M. COPPIN**[1], G. CHANGARATHIL[1], P. VARMA[1], Z. LYBRAND[2], A. ADEYEYE[1], J. HSIEH[1];
[1]Neuroscience, Regenerative, and Developmental Biol., Univ. of Texas at San Antonio, San Antonio, TX; [2]Biol., Texas Woman's Univ., Denton, TX

**Abstract:** Studies show seizure induced aberrant hippocampal neurogenesis contribute to the development of chronic seizures. Our lab reported that 2-week-old (2w) adult-born granule cells (abGCs) in the mouse dentate gyrus display elevated $Ca^{2+}$ activity after pilocarpine (pilo) induced seizures compared to sham. Moreover, this amplified $Ca^{2+}$ activity is reduced by chemogenetic DREADDs/hM4Di silencing in pilo treated mice. The molecular mechanisms by which elevated $Ca^{2+}$ activity drives aberrant hippocampal neurogenesis and, in turn, epileptogenesis is unknown. Hence, we hypothesize that early activity in abGCs alters $Ca^{2+}$ mediated gene expression that promote aberrant maturation, including ectopic migration of abGCs associated with spontaneous recurrent seizures. RNA-sequencing analysis from FACS sorted 2w old abGCs after pilo treatment and hM4Di silencing revealed differentially expressed genes, i.e., gene expression downregulated with pilo treatment and upregulated with hM4Di silencing, among which *Timp3* was one of the most significantly differentially expressed genes. Because *Timp3* is widely reported to regulate migration and invasion of tumor cells by modifying matrix metalloproteinases, we hypothesized that seizure induced changes in the expression of *Timp3* may play a role in controlling aberrant abGC migration. First, we confirmed in RNAscope analysis that *Timp3* is expressed in abGCs which is downregulated in pilo treated mice. To determine the role of *Timp3* in aberrant abGC development, we used the LXR agonist T0901317 reported to knockdown its expression. Treatment of mice with T0901317 for 2w resulted in an increased number of hilar ectopic abGCs and granule cell dispersion. These results suggest that alterations in $Ca^{2+}$activity within 2w old abGCs after pilo leads to changes in gene expression, including *Timp3,* which could play a role in aberrant migration of abGCs. Furthermore, our preliminary experiments suggest that T0901317 mediated downregulation of *Timp3* leads to non-convulsive seizures in mice. Our work also demonstrates a new way to manipulate potential aberrant gene regulatory pathways and define the functional role of our top candidate gene - *Timp3* - in aberrant adult neurogenesis. Future experiments aim to address the function of *Timp3* in generating seizure-like activity by using human embryonic stem cell-derived cortical and subpallial organoids.

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**Poster**

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**Topic:** B.08. Epilepsy

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NIH Grant 1F99NS129126-01A1

**Title:** Sodium-dependent citrate transporter (SLC13A5) mutant mice indicate that dysfunction is not limited to transporter deficiency

**Authors: *K. A. DE LEON**[1], L.-J. CHEW[2], H. HIGASHIMORI[3], K. WHITLEY[6], A. ZENG[4], J. S. LIU[5];
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**Abstract:** Mutations in the SLC13A5 gene, which encodes a plasma membrane citrate transporter, result in early infantile epileptic encephalopathy (EIEE25), a neonatal neurological disorder characterized by multi-focal seizures, severe hypotonia and intellectual delay. Human genetics has identified commonly occurring deletion and missense mutations that abolish citrate transport by SLC13A5, but it is not known how distinct mutations cause disease. To determine whether missense mutants show features of SLC13A5 deficiency, we embarked on the characterization of an array of SLC13A5 mutant mice: i) ablation of endogenous Slc13a5 gene (null), two of the most frequently occurring patient missense mutations- ii) G222R mutation (equivalent to human G219R mutation), and iii) T230M (mouse equivalent of human T227M mutation). Our epileptiform electroencephalogram (EEG) analysis indicates that the Slc13a5 null mouse shows few seizures with abnormal spike activity that is not statistically different from wild type (WT) control. G222R and T227M mice however display significantly more interictal spiking activity, with >50% mice showing status epilepticus at 2 and 3 months. This indicates a disease pathogenesis that is distinct from the absence of SLC13A5. These functional changes are correspondingly associated with cellular abnormalities that are most significant in G222R, followed by T230M, including reduced parvalbumin interneurons in CA1 compared with WT and null. MAG and CC1 oligodendrocytes in G222R and T227M white matter are also reduced compared with WT and SLC13A5 null, while astrocytes and CAMKII excitatory neurons appear unaffected across SLC13A5 mutants. Preliminary morphological analysis of cortical neurons cultured from G222R mice revealed reduced neurite length and branching, suggesting aberrant development. Recombinant human WT and SLC13A5 T227M mutant proteins are localized at the plasma membrane of cultured mouse cortical and hippocampal neurons while G219R mutant protein is primarily detected with GP96 chaperone in endoplasmic reticulum. Similar observations were obtained in mouse astrocytes and HEK293T cells. These results indicate that

neuronal hyperactivity is differentially regulated by distinct SLC13A5 mutations. Our observations support the notion that loss of SLC13A5 underlies epileptiform activity, but specific missense mutations may increase neuronal vulnerability through additional mechanisms that exacerbate hyperexcitability.

**Disclosures: K.A. De Leon:** None. **L. Chew:** None. **H. Higashimori:** None. **K. Whitley:** None. **A. Zeng:** None. **J.S. Liu:** None.

**Poster**

**PSTR009. Animal Models of Epilepsy: Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR009.11/D10

**Topic:** B.08. Epilepsy

**Support:** 1R01NS092705
1R01NS107453
R21NS126740

**Title:** Mir-324-5p inhibition during epileptogenesis in mice alters eeg power bands during disease progression.

**Authors: *A. MCGANN**[1,4,5], G. C. WESTERKAMP[2], A. CHALASANI[1], C. S. K. DANZER[1], P. S. HORN[1,6], E. V. PEDAPATI[2], D. TIWARI[1,6], S. C. DANZER[3,4,5,7], C. GROSS[1,6,4,5]; [1]Div. of Neurol., [2]Div. of Child Psychiatry, [3]Dept. of Anesthesia, Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH; [4]Med. Scientist Training Program, [5]Neurosci. Grad. Program, [6]Dept. of Pediatrics, [7]Dept. of Anesthesiol., Univ. of Cincinnati, Cincinnati, OH

**Abstract:** Rationale: Epilepsy is often caused by an initial brain insult that is followed by epileptogenesis and finally the development of spontaneous recurrent seizures. The details underlying epileptogenesis remain largely unknown. MicroRNAs regulate mRNA translation and stability and are often altered in epilepsy. Antagonism of a specific miRNA, miR-324-5p, before brain insult and in a model of chronic epilepsy has been shown to decrease seizure susceptibility and frequency. Here we tested the hypothesis that antagonism of miR-324-5p inhibits epileptogenesis following a brain insult. Methods: We used the intrahippocampal kainic acid (IHpKa) model to induce *status epilepticus* and initiate epileptogenesis in 43 wild type male C57/Bl6 mice aged 6-8 weeks. Twenty-four hours after kainic acid injection, we administered a miR-324-5p (21 mice) or scrambled control (22 mice) antagomir intracerebroventricularly and implanted cortical surface electrodes for EEG monitoring. EEG data was collected for 28 days and analyzed for seizure frequency and duration. In addition, we analyzed interictal spike activity and EEG power at early (days 7-9 post-Ka) and later (days 25-27 post-Ka) stages of the disease progression. Mouse brain tissue was collected for assessment of dentate granule cell dispersion and CA1 cell death. The study was exploratory in nature, specifically assessing the effect of miR-324-5p inhibition during epileptogenesis. Results: IHpKa reliably initiated

epileptogenesis. Histological analysis showed that IHpKa caused hippocampal damage characteristic of the model in the majority of mice and that the extent of the injury did not vary based on treatment. EEG analyses showed that antagomir treatment did not affect latency, frequency, or duration of spontaneous recurrent seizures or frequency of interictal spikes or spike trains. Antagomir treatment did, however, alter EEG power of specific frequency bands over time with significant interactions between time and treatment for the absolute power of select frequency bands: delta, theta, alpha, beta, and gamma 1. Conclusions: Overall, our results suggest that while miR-324-5p inhibition does not inhibit the development of spontaneous seizures within the first four weeks after *status epilepticus*, it may change overall brain excitability, which could affect seizures and related brain function at later stages of the disease.

**Disclosures: A. McGann:** None. **G.C. Westerkamp:** None. **A. Chalasani:** None. **C.S.K. Danzer:** None. **P.S. Horn:** None. **E.V. Pedapati:** None. **D. Tiwari:** None. **S.C. Danzer:** None. **C. Gross:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US patent 9,932,585 B2.

**Poster**

**PSTR009. Animal Models of Epilepsy: Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR009.12/D11

**Topic:** B.08. Epilepsy

**Support:** CIHR PJT-162204

**Title:** Modulation epileptogenesis with cannabinoids in the SSP-Saporin "Trojan Horse" model

**Authors: *S. GUPTA**[1], M. KESLER[1], M. H. SCANTLEBURY[1], R. S. SLOVITER[3], G. TESKEY[2];
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**Abstract:** Epilepsy is a chronic condition characterized by repeated self-generated seizures. Epileptogenesis is a dual process whereby seizure thresholds lower to the point where self-generated seizures are observed as well as the increase in frequency, duration, and severity of seizures. Epileptogenesis is a serious health problem with no effective treatment. Here we exploited a new animal model of epileptogenesis that selectively kills GABAergic interneurons in the dentate hilar area leading to a cascade of events which induces epileptogenesis and dentate initiated seizures without behavioural status epilepticus and associated lethality. This was done by injecting the selective neurotoxin: Saporin conjugated with Stabilized Substance P (SSP-SAP) (0.04 ng/nL) at four longitudinal sites in the hilar region of the rat hippocampus to selectively ablate inhibitory interneurons. During the same surgery, rats also received chronically implanted bipolar recording electrodes in the granule cell layer.
The endocannabinoid system dampens neuronal activity and thus may aid in slowing or

prevention of epileptogenesis. Specifically, the CB1 receptor and its endogenous ligands are found abundantly in the hippocampus and have been demonstrated to modulate temporal lobe seizures. Young adult Sprague Dawley rats received either the CB1 agonist WIN55 212-2 (2 mg/mL, i.c.v.) or the FAAH inhibitor URB597 (8.3 mg/mL, i.c.v.) or vehicle immediately after SSP-SAP administration through an indwelling cannula to the lateral ventricle over a 2-week period via an osmotic minipump. Continuous 24-hour video-EEG was recorded for all rats for a period of 2-weeks. Afterwards, all brains were extracted and examined for hippocampal sclerosis (loss of principle excitatory cells and astrogliosis). Epileptiform activity was observed a day after SSP-SAP administration. Behavioural seizures with associated epileptiform discharges were typically observed on day 4 through 7, while epileptiform activity continued to occur. The behavioural seizures were again observed after approximately one month. Our preliminary results with the WIN55 212-2 and URB597 show reduced number of behavioural and associated electrographic seizures within the first 2 weeks. Overall, administration of SSP-SAP to the rat dentate hilar area results in epileptogenesis and a CB1 agonist and FAAH inhibitor both slowed down its progression.

**Disclosures: S. Gupta:** None. **M. Kesler:** None. **M.H. Scantlebury:** None. **R.S. Sloviter:** None. **G. Teskey:** None.

**Poster**

**PSTR009. Animal Models of Epilepsy: Mechanisms**

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**Program #/Poster #:** PSTR009.13/D12

**Topic:** B.08. Epilepsy

**Support:** R01NS122782
T32-GM007055-29

**Title:** Microglia play beneficial roles in multiple experimental seizure models

**Authors: *S. GIBBS**[1], J. BENDEROTH[2], J. UWERU[4], R. GAYKEMA[3], E. PEREZ-REYES[5], U. B. EYO[5];
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**Abstract:** Seizure disorders are common, affecting both the young and the old. Currently available antiseizure drugs are ineffective in a third of patients and have been developed with a focus on known neurocentric mechanisms, raising the need for investigations into alternative and complementary mechanisms that contribute to seizure generation or its containment. Neuroinflammation, broadly defined as the activation of immune cells and molecules in the central nervous system (CNS), has been proposed to facilitate seizure generation, although the specific cells involved in these processes remain inadequately understood. The role of microglia,

the primary inflammation-competent cells of the brain, is debated since previous studies were conducted using approaches that were less specific to microglia or had inherent confounds. Using PLX3397, a selective approach to target microglia without such side effects, we show a broadly beneficial role for microglia in limiting chemoconvulsive, electrical, and hyperthermic seizures and argue for a further understanding of microglial contributions to contain seizures.

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**Poster**

**PSTR009. Animal Models of Epilepsy: Mechanisms**

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**Program #/Poster #:** PSTR009.14/D13

**Topic:** B.08. Epilepsy

**Support:** NIH HL122358 (MRH)
DK126720 (OP)
HL135749 (AS)

**Title:** Effects of seizures on cardiorespiratory control and mortality in the $SS^{Kcnj16-/-}$ rat

**Authors: *M. EILBES**[1], A. D. MANIS[2], V. LEVCHENKO[3], H. V. FORSTER[2], O. PALYGIN[4], A. STARUSCHENKO[3], M. R. HODGES[1];
[1]Physiol., [2]Med. Col. of Wisconsin, Milwaukee, WI; [3]Univ. of South Florida, Tampa, FL; [4]Med. Univ. of South Carolina, Charleston, SC

**Abstract:** Repeated, uncontrolled seizures put patients at risk for cardiorespiratory failure (CRF) and Sudden Unexpected Death in Epilepsy (SUDEP). The mechanism(s) leading to CRF remain unclear and there are no established ways to predict or prevent SUDEP. Humans have a nocturnal susceptibility to SUDEP, which is thought to occur following generalized tonic-clonic seizures (GTCS), which then leads to post-ictal EEG suppression, central apnea, bradycardia, and terminal apnea/asystole. Here we studied seizure-related death events in a rat model susceptible to audiogenic GTCSs ($SS^{Kcnj16-/-}$ rats) in which we have shown previously that repeated seizures (1/day for up to 10 days) in this model leads to ictal apnea, progressive post-ictal respiratory suppression, and increased mortality. We tested the hypothesis that repeated seizures in $SS^{Kcnj16-/-}$ rats results in CRF that follows a sequence of events like those in human SUDEP. Male and female $SS^{Kcnj16-/-}$ rats were implanted with a pressure telemeter and housed in a chronic monitoring plethysmograph to continuously measure breathing, blood pressure (BP) and heart rate (HR). The rats were exposed to an audio stimulus (2 mins) shortly before the onset of the dark (active) period to elicit 1 seizure a day for up to 10 days. As shown before, repeated GTCSs induced ictal apnea/asystole followed by decreased HR, increased BP and ventilatory suppression. These studies also documented CR dysfunction leading up to seizure-related death events in this model for the first time. $SS^{Kcnj16-/-}$ females had a 14% survival probability (12 of 14

died) when seizures occurred shortly before the onset of the dark phase compared to our previously reported 88% survival rate (1 of 8 died) throughout the light phase. Characteristics of these death events included a steady decline in BP with an elevated HR over ~2 hrs post-ictal. We also noted a breathing pattern (tidal volume and total ventilation below baseline with normal ventilatory rate) prior to simultaneous terminal apnea/asystole. Our data suggest that repeated seizures in this model may induce CRF through post-ictal respiratory suppression (tidal volume-mediated hypopnea) and progressive hypotension leading to death, where time of day for seizure induction/death likely contributed to a higher mortality rate, particularly in females. This model may therefore be useful towards the ultimate goal of identifying biomarkers to reduce the risk of SUDEP in patients with epilepsy.

**Disclosures: M. Eilbes:** None. **A.D. Manis:** None. **V. Levchenko:** None. **H.V. Forster:** None. **O. Palygin:** None. **A. Staruschenko:** None. **M.R. Hodges:** None.

**Poster**

**PSTR009. Animal Models of Epilepsy: Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR009.15/D14

**Topic:** B.08. Epilepsy

**Support:** CONACYT doctoral scholarship 960415 awarded to DACR
Cuerpo Académico de Neurofisiología (UV-CA-333)

**Title:** Maternal restraint stress during pregnancy enhances neonatal status epilepticus-induced neuronal injury in rats

**Authors: *L. LOPEZ-MERAZ**[1], D. CRUZ ROJAS[1], B. MARTÍNEZ-ROJAS[1], L. BELTRÁN-PARRAZAL[1], C. MORGADO-VALLE[2];
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**Abstract:** Evidence shows that maternal prenatal stress may affect early brain development in the offspring. Our previous results showed that neonates from stressed mothers displayed higher status epilepticus (SE) severity than control rats. The goal of this study was to evaluate the effect of maternal restraint stress during pregnancy on neonatal SE-induced brain injury in rats. Gestational stress was induced by immobilization of pregnant Wistar rats from gestation days 12 to 20, twice a day during two 2 h sessions. Control rats were kept in standard housing conditions. On postnatal day 7, SE was induced with the lithium-pilocarpine model (LiCl 5mEq/kg, i.p.; pilocarpine hydrochloride 320mg/kg, s.c.). 24 h after SE, rats were anesthetized and transcardially perfused with 0.9% NaCl and 4% paraformaldehyde. Brains were paraffin-embedded, and coronal sections (10μm thickness) were obtained and mounted on gelatin-coated slides. Neurodegeneration was assessed by Fluoro-Jade C staining. The results showed that neonates from stressed mothers had higher neurodegeneration scores than control rats in several

brain areas including the motor cortex, CA1, CA2, and CA3 hippocampal fields, the basolateral amygdala, the ventral and lateral thalamus, and the hypothalamus. Male rats showed more injured brain areas than female rats. In conclusion, our data suggest that maternal stress during pregnancy has a negative impact on the offspring favoring seizure susceptibility and neurodegeneration.

**Disclosures: L. Lopez-Meraz:** None. **D. Cruz Rojas:** None. **B. Martínez-Rojas:** None. **L. Beltrán-Parrazal:** None. **C. Morgado-Valle:** None.

**Poster**

**PSTR009. Animal Models of Epilepsy: Mechanisms**

**Location:** WCC Halls A-C

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**Topic:** B.08. Epilepsy

**Support:** NIH Grant NS107148
NIH Grant R01NS079507
NIH Grant R01AG075583
NIH Grant R21NS131903

**Title:** Modeling rat seizure onset dynamics from non-invasive motion signals for screening

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**Abstract:** Preclinical research is a vital step in the development of treatment for epilepsy that aims to reduce seizure burden. Currently, the gold standard for detecting seizures in animal models is invasive EEG analysis, which is time- and resource-intensive. Non-invasive seizure screening methods are available but have limited specificity as they rely on movement and other behavioral measures of seizures rather than the neural activity at the source. This leads to a higher false positive detection rate when compared to invasive EEG analysis. To reduce this false positive detection rate, we used the dynamics of seizure onset as captured by piezoelectric (‘piezo’) motion sensors to create machine learning models for the rodent model of temporal lobe epilepsy. All tasks performed in this study were approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Kentucky. Wistar rats (n=24) treated with lithium-pilocarpine were monitored continuously for several weeks using piezo platforms (Signal Solutions, LLC) under the cage floor. The recorded signals were processed using a line length-based algorithm that responds to fluctuations in power to produce an initial set of candidate seizures. We then manually reviewed video data to label each of these events as true seizure (rated 3-5 on the Racine scale) or false positive. Normal behavior occurring at the same time in neighboring cages were extracted as interictal baseline samples. Thirty-second-long segments of

piezo signals centered on the initial event detection times were extracted for 500 random events of each type (total 1500). Four features representing measures of signal power, variance, and entropy were computed from each segment from one second windows with a 0.5 second overlap. Two data-driven dynamical models, one a Long Short-Term Memory (LSTM) neural network, and the other a Hidden Markov Model (HMM), were fitted to a continuous and discretized feature vector time series, respectively. The models were trained and tested using a 10-fold cross validation scheme. Model performance was evaluated in terms of the F1 score - a measure of accuracy that combines precision and recall - and specificity. Mean F1 scores were 70±1% and 52±3%, while mean specificities were 82±1% and 59±7% for the LSTM and HMM, respectively. The performance of our models shows that seizure-related movement dynamics may be consistent enough for seizure detection with greater specificity than simple signal power-based methods. We plan to compare our models against static classifiers to test whether this translates into gains in specificity, and to apply them to continuous, chronic data rather than isolated segments.

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**Poster**

**PSTR009. Animal Models of Epilepsy: Mechanisms**

**Location:** WCC Halls A-C

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**Topic:** B.08. Epilepsy

**Support:** Australian Research Council's Training Centre in Cognitive Computing for Medical Technologies IC170100030

**Title:** Critical slowing down in the rat tetanus toxin model of epilepsy

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**Abstract:** Several studies have shown that EEG signals recorded from the brain, like other dynamical systems, exhibit critical slowing down before critical transitions, such as seizures (Maturana et al. 2020). Here, we used intracranial EEG data recorded from tetanus toxin rat model of epilepsy. Tetanus toxin has been shown to induce spontaneous seizures in rodents that wax and wane over a period of around 6 weeks. The response to periodic electrical stimulation was recorded along with the background intracranial EEG in six rats (Crisp et al. 2020). We fitted the parameters of a neural mass model to the background EEG, allowing us to analyze the response of the model neurons to stimulation and investigate the critical slowing down biomarker for seizure prediction.The neural mass model developed for this study consists of three interconnected layers representing a cortical column: layers 2/3, 4, and 5 (Zarei Eskikand et

al. bioRxiv 2022). Each layer contains one population of excitatory neurons and one population of inhibitory neurons. We employed an Unscented Kalman Filter to fit the connectivity weights of the model to the background EEG data recorded from rats. Once the connectivity weights were optimized to fit the background EEG data, we simulated the model and applied stimulation to the neuronal populations at each layer to observe their responses. The recovery time, defined as the time from stimulation until the membrane potential returns to 1% of baseline, was measured.The results revealed that recovery times in the responses of the computational model fitted to the EEG data were longer during 5 min periods preceding seizures compared to 1 hr before seizures in four rats. However, for two rats (T4 and T6), opposite results were observed. Analyzing the EEG recorded in response to electrical stimulation also showed that the recovery time during the 5 min preictal period was longer compared to the period within 1 hr before a seizure in the same four rats as the computational model results. Interestingly, for rat T4, the recovery times were longer within 1 hr before seizures, similar to the computational model results. On the other hand, the results for rat T6 indicated that the recovery times were longer during the 5 min preictal period compared to 1 hr before seizures, contradicting the modelling results.The critical slowing down phenomenon was observed in the EEG data recorded from four of six rats in response to electrical stimulation. The results of the data-driven model aligned with these findings in five rats. This study underscores the significance of computational models in enhancing our understanding of complex neurological disorders such as epilepsy.

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**Poster**

**PSTR009. Animal Models of Epilepsy: Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR009.18/D17

**Topic:** B.08. Epilepsy

**Title:** Supervised classification of continuous video-EEG yields a reliable method for classifying behavioural states in rodents.

**Authors: *J. O'BRIEN-CAIRNEY**[1], M. UPADHYA[1], H. PRÜSS[2,3], D. SCHMITZ[2,3], H.-C. KORNAU[2,3], G. WOODHALL[1], B. ZAAIMI[1], S. WRIGHT[1], R. ROSCH[4];
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**Abstract:** Purpose:
Patients diagnosed with various forms of epilepsy, including autoantibody-associated epilepsies as seen in anti-leucine-rich glioma-inactivated 1 (LGI1) encephalitis, often present with comorbid sleep disorders. Patients with LGI1-Abs and seizures show reductions in sleep time

and architecture. However, it remains unclear as to when, during the course of the encephalitis, these sleep disorders develop, as recording patients continuously is difficult. We therefore seek to use data available from a novel passive-transfer model to quantify changes in resting patterns in anti-LGI1 encephalitis.
Methods:
Video-EEG telemetry recordings were performed in a passive transfer model of anti-LGI1 encephalitis in P21 Wistar rats using the Neuroarchiver software (Open Source Instruments). 1271 eight-second epochs of wakeful and resting behaviour, defined as the rat being immobile and having closed eyes for at least 40 seconds, among control-Ab-treated rats (n=5) and LGI1-Ab-treated rats (n=5) were visually classified. Support vector machines were used to predict the behavioural state of each rat during each epoch throughout seven days based on the epochs of hippocampal EEG recordings, with manually labelled classification from video-EEG data being the gold standard. The accuracy of our predictions was determined systematically by training the classifier on a random 80% of our labelled data and testing it on the remaining 20%, which was repeated using 1000 iterations.
Results:
Our receiver operator characteristic (ROC) analysis showed that our classifier yielded an average accuracy of 83-87%. Our control rats, after the residual effect of the anaesthetic and surgery had waned, showed clear diurnal variation in total rest time (TRT) per hour with a midday maximum. Restful behaviour on average lasted over longer consecutive epochs during daytime compared to the night ($p=0.0157$). The rodents rested for shorter consecutive intervals than previously described. However, the polyphasic nature of our rodent model's rest patterns is congruent with previous work. Using these quantitative parameters, we tested for statistically significant differences in total rest time and in the fragmentation and diurnal variation in resting behaviour between controls and LGI1-Ab-treated rats.
Conclusion:
Our visually labelled behavioural data was sufficient to quantify longitudinal changes in control rats. This method allows for the quantitative analysis of changes in resting behaviour, which in future can be applied to quantitatively characterise behavioural state alterations during disease progression in novel disease models, such as the LGI1-Ab rats.

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**Poster**

**PSTR009. Animal Models of Epilepsy: Mechanisms**

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**Topic:** B.08. Epilepsy

**Support:** AES Research & Training Fellowships for Clinicians
NIH Grant 5T32GM139799-02
AES Grant 980019

**Title:** An evalution of Convolution Detection Methods for Neurostimulation Artifact Removal

**Authors: *D. CAMACHO**[1], N. RENSING[2], T. J. FOUTZ[2];
[1]Mathematics, Brigham Young Univ., Provo, UT; [2]Washington Univ. in St. Louis, Saint Louis, MO

**Abstract:** Rationale: Neurostimulation is increasingly used to treat drug-refractory epilepsies. Tuberous sclerosis (TSC) is one of the most common single-gene disorders associated with epilepsy, often complicated by drug-refractory focal epilepsy. The Tsc1GFAPCKO mouse model has been developed to better understand the mechanisms and potential treatments of epilepsy in TSC, including abnormal neuronal growth and seizures. Our group has been using this model to evaluate the effects of neurostimulation; however, acquiring EEG and EMG data during neurostimulation trials is difficult due to stimulation artifacts; removing this is critical to evaluate the effects of neurostimulation on normal brain physiology and seizures.
Methods: A bandpass filter was first applied to the EEG/EMG signal. To isolate the timing of the stimulation artifact in the EEG/EMG signal, the signal was convolved with a variety of kernels with trains of different pulse shapes, including sine, uniphasic Dirac, and biphasic Dirac, each with a kernel width of 30 seconds. After detecting the stimulation artifact, it was removed, and the residual stimulation artifact signal was quantified. After identifying the kernel shape with the minimal average residual artifact, the EEG/EMG signal was again convolved using this optimal shape across a range of kernel widths (10-150 sec) to optimize its width.
Results: For a kernel width of 30 sec, the average duration of the residual stimulation artifact was 1.57 (SD 3.17), 1.44 (SD 3.08), and 1.17 sec (SD 2.79) for the sine wave, uniphasic Dirac, and biphasic Dirac kernels, respectively. The biphasic Dirac kernel was the most sensitive, with 12,641 detections, followed by uniphasic Dirac (12,598) and sine (12,539). The biphasic Dirac demonstrated both the lowest average duration of residual stimulation artifact and was the most sensitive. The average residual stimulation artifact duration for this kernel was minimized when using a 10-second convolution kernel width.
Conclusions: The most effective combination observed for removing the stimulation artifact in EEG and EMG signals was found to be a biphasic Dirac convolution with a kernel width of 10 seconds. It is hypothesized to be optimal because shorter kernels overemphasize anomalies, while larger kernels reduce signal strength. These findings provide valuable insights into improving the process of EEG/EMG signal cleaning, specifically for removing stimulus artifacts. These improvements will facilitate the evaluation of the effects of neurostimulation on normal brain physiology and seizures.

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**Poster**

**PSTR010. Oligodendrocyte Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR010.01/D19

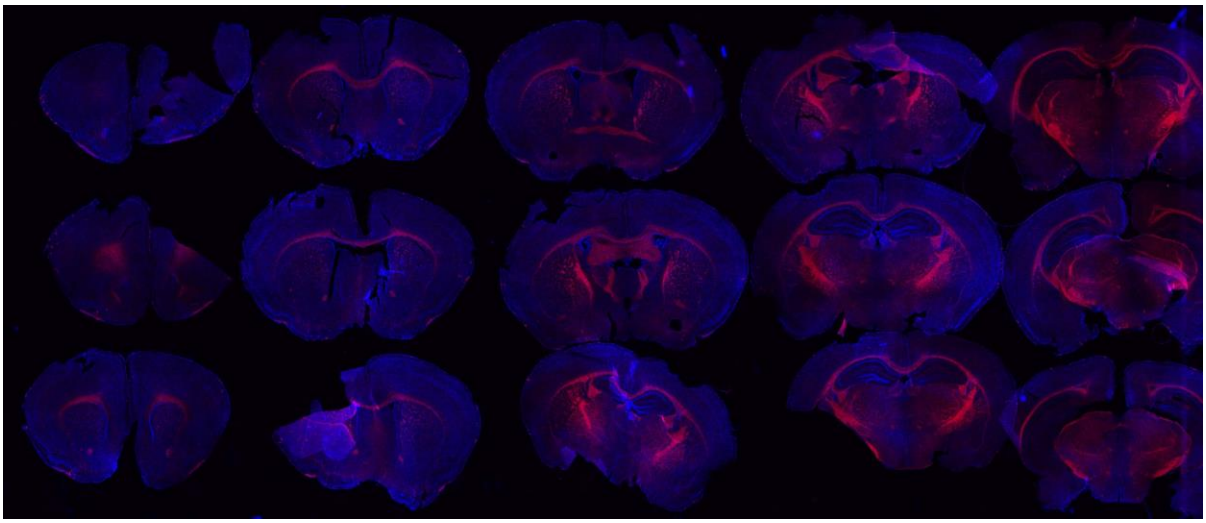
**Topic:** B.09. Glial Mechanisms

**Support:** MathWorks Science Fellowship at MIT
Collamore-Rogers Fellowship at MIT
National Science Foundation Graduate Research Fellowship Grant 1745302
NIH Grant 1F31MH133329-01

**Title:** Gpr17-IRES-Cre, a novel constitutive Cre driver line specific to the oligodendrocyte lineage and a subset of astrocytes

**Authors:** M. E. SCHROEDER, ***L. METZNER**, D. MCCORMACK, P. A. YOUNG, G. FENG;
Brain & Cognitive Sci., MIT, Cambridge, MA

**Abstract:** In the central nervous system, mature, myelinating oligodendrocytes differentiate from oligodendrocyte precursor cells. The precise study of the distinct molecular functions of this glial lineage is critical for investigating their roles in neurotransmission, plasticity, and response to brain injury and disease (Levine et al., 2001, Mount and Monje, 2017). Investigation of this lineage has been limited by a lack of specific and sensitive genetic tools. In particular, existing Cre-driver mouse lines targeting the oligodendrocyte lineage exhibit off-target expression in other neuronal and glial cell populations, including motor neurons in Olig2-Cre (Kessaris et al., 2005) or pericytes in Ng2-Cre (Zhu et al., 2008). Alternatively, inducible CreERTM lines require the administration of tamoxifen, a hazardous drug whose administration in neonates may adversely affect development. We used CRISPR-Cas gene editing to generate a novel mouse line constitutively expressing Cre-recombinase from the locus of Gpr17, a gene whose expression is restricted to the oligodendrocyte lineage in the postnatal CNS (Chen et al., 2009). Using crossbreeding with a transgenic reporter mouse line, we demonstrate that Gpr17-Cre expresses Cre-recombinase in the majority of oligodendrocyte lineage cells and a small subset of astrocytes (Fig. 1). We compare Gpr17-Cre and Olig2-Cre sensitivity and specificity in the brain and spinal cord by co-staining for markers of oligodendrocyte, OPC, neuronal, and astrocytic identity. We will present the results of blinded, automated cell counting from confirmatory studies to quantitatively compare the specificity and sensitivity between the two lines (n = 5 animals per genotype, including both males and females). This novel mouse line will enable sensitive and specific observation and manipulation of oligodendrocyte lineage cells without temporal induction, allowing improved dissection of their development and function in health and disease.
Figure 1. Endogenous tdTomato signal (red) and DAPI (blue) staining in a Gpr17-Cre;Ai14 mouse perfused at P20.



**Disclosures:** **M.E. Schroeder:** None. **L. Metzner:** None. **D. McCormack:** None. **P.A. Young:** None. **G. Feng:** None.

**Poster**

**PSTR010. Oligodendrocyte Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR010.02/D20

**Topic:** B.09. Glial Mechanisms

**Support:** Robert J. and Nancy D. Carney Endowment, P20GM103645

**Title:** Pdgf signaling in opcs is necessary for complete opc occupation of the cns

**Authors: *S. FREGOSO**[1], M. MCQUILLAN[2], S. RIOS MENDEZ[3], M. SALEEM[1], G. MOLICA[1], J. AGUILERA[1], A. BHAGWAT[1], C. CALL[1], S. R. MAYORAL[2];
[2]Neurosci., [1]Brown Univ., Providence, RI; [3]Brown Univ. Neurosci. Grad. Program, Providence, RI

**Abstract:** Myelin is an insulating sheath that wraps axons and is critical for proper nervous system function in vertebrates. In the central nervous system (CNS), myelin is made by specialized glial cells known as oligodendrocytes (OLs). OLs differentiate from OL precursor cells (OPCs), which are highly proliferative and motile cells that populate the entire CNS in early development. OPCs display the tyrosine kinase receptor-platelet derived growth factor receptor alpha (PDGFRa)-that binds to the mitogen PDGF-A. PDGF-A promotes the survival, proliferation and motility of OPCs. In order to better study the role of PDGF signaling in OPCs during early development, we used Cre-lox methods to specifically knock out PDGFRa in OPCs. Using immunohistochemistry and fluorescence imaging analysis, we examined OPC and OL densities, and myelination throughout the CNS in conditional PDGFRa KOs (PDGFRa cKOs)

and littermate controls. While the development of oligodendroglia appeared normal across most of the CNS, we found that certain regions lacked OPCs, OLs, and myelin in PDGFRa cKOs. These results suggest that PDGF signaling is necessary for complete OPC occupation of the CNS and we present a novel mouse model for examining the regional absence of oligodendroglia.
Funding: Robert J. and Nancy D. Carney Endowment, P20GM103645

**Disclosures:** **S. Fregoso:** None. **M. McQuillan:** None. **S. Rios Mendez:** None. **M. Saleem:** None. **G. Molica:** None. **J. Aguilera:** None. **A. Bhagwat:** None. **C. Call:** None. **S.R. Mayoral:** None.

**Poster**

**PSTR010. Oligodendrocyte Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR010.03/D21

**Topic:** B.09. Glial Mechanisms

**Support:** NIH Grant NS105689

**Title:** The PERK-eIF2α pathway in mature oligodendrocytes controls myelin thickness in the adult CNS by regulating myelin protein translation

**Authors: *W. LIN**, S. WU;
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**Abstract:** The main function of oligodendrocytes is to assemble and maintain myelin that wraps and insulates axons in the CNS. Myelin structure, including thickness, was thought to be extraordinarily stable in adults. Intriguingly, emerging evidence suggests that the thickness of myelin can be changed dynamically in the adult CNS, contributing to myelin plasticity. Nevertheless, the mechanisms governing myelin thickness in the adult CNS remain elusive. Upon ER stress, activation of PERK adapts cells to stressful conditions by phosphorylating eIF2α, which suppresses global protein translation but stimulates certain cytoprotective gene expression. Interestingly, we found that impaired ERAD in oligodendrocytes via Sel1L knockout in *CNP/Cre*; *Sel1L*$^{loxP/loxP}$ mice does not affect developmental myelination, but leads to late-onset, progressive myelin thinning in the CNS of adult mice, which is accompanied with PERK activation and attenuation of myelin protein translation. Using an inducible Sel1L knockout mouse model (*PLP/CreER*$^{T}$; *Sel1L*$^{loxP/loxP}$ mice), we further found that Sel1L knockout in mature oligodendrocytes leads to PERK activation, attenuation of myelin protein translation, progressive myelin thinning in the adult CNS. Moreover, we found that PERK inactivation in oligodendrocytes reverses attenuation of myelin protein translation in oligodendrocytes and restores myelin thickness in the CNS of *CNP/Cre*; *Sel1L*$^{loxP/loxP}$ mice. Importantly, using *PLP/Fv2E-PERK* mice that allow for temporal activation of PERK specifically in oligodendrocytes by administration of AP20187, we showed that PERK activation in mature oligodendrocytes suppressed myelin protein translation and led to myelin thinning but no

oligodendrocyte loss in the CNS of adult mice. Collectively, the findings suggest that the PERK pathway in mature oligodendrocytes controls myelin thickness in the adult CNS by regulating myelin protein translation.

**Disclosures: W. Lin:** None. **S. Wu:** None.

**Poster**

**PSTR010. Oligodendrocyte Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR010.04/D22

**Topic:** B.09. Glial Mechanisms

**Support:** DOD Grant 13212139

**Title:** C1ql1 protein promotes maturation of oligodendrocytes

**Authors: *S. ALAM**[1], Z. ALTUNAY[1], J. BISWAS[1], H. CHEUNG[1], R. PIJEWSKI[1], A. SCHOUW[1], A. NISHIYAMA[2,3], S. J. CROCKER[1,3], D. MARTINELLI[1,3];
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**Abstract:** C1QL1 protein promotes maturation of oligodendrocytes.Shahnawaz Alam[1], Zeynep M. Altunay[1], Joyshree Biswas[1], Hiu Cheung[1] , Robert S. Pijewski[1], Alexander D. Schouw[1], Akiko Nishiyama[1-3], Steve J. Crocker[1,3], David C. Martinelli[1,3,*]
1Department of Neuroscience, University of Connecticut Health, Farmington CT 06030 USA2Department of Physiology and Neurobiology, University of Connecticut, Storrs, CT 06269, USA3The Connecticut Institute for the Brain and Cognitive Sciences (IBACS)Central nervous system (CNS) myelin is made by a specialized class of glia cell called oligodendrocytes and is crucial for brain development and cognitive function. Oligodendrocyte precursor cells (OPCs) have the capacity to regenerate oligodendrocytes and myelin. The mechanism which underlies the maturation of OPCs into mature oligodendrocytes is poorly understood. Previous studies have shown that alteration in glia-glia communication may underlie the failure of remyelination in multiple sclerosis (MS). Multiple members of the C1q/TNF superfamily of proteins are involved in the regulation of synaptic organization and functions in various brain regions. C1Q-like (*C1QL*) proteins bind to the adhesion G protein-coupled receptor GPCR B3 (ADGRB3; a.k.a. BAI3) and act at synapses but its possible role in OPC maturation into oligodendrocytes has not yet been investigated. Therefore, in the present study, we have investigated the role of C1QL1 protein in regulating OPC maturation in vitro. To study the mechanism which underlies C1QL1 influence over OPC maturation, we prepared primary OPC cultures from neonatal rats via an immuno-panning method. A purified recombinant C1QL1 protein was added to experimental wells. We found that C1QL1 caused a significant increase in the fraction of OLIG2-positive cells which differentiated into mature oligodendrocytes,

supporting our hypothesis that C1QL1 can promote the maturation of OPCs. We further investigated if C1QL1 can signal to astrocytes, which express ADGRB3. We found that application of C1QL1 to primary astrocyte cultures causes astrocytes to upregulate the secretion of several factors which were previously shown to regulate OPC maturation. Our results suggest that C1QL1 can cause an increased fraction of OPCs to mature into oligodendrocytes, and that this may involve C1QL1 signaling to astrocytes.Supported by: Department of Defense, Multiple Sclerosis Research Program (Grant:13212139), Award number: W81XWX-21-1-0707/A

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**Poster**

**PSTR010. Oligodendrocyte Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR010.05/D23

**Topic:** B.09. Glial Mechanisms

**Support:** NS 37 NS82203

**Title:** Unexpected role of neuronal activity in early oligodendrocyte development

**Authors: *T. ALLEN**[1], K. GIVEN[2], W. OH[3], W. B. MACKLIN[2];
[1]Univ. of Colorado, Anschutz Med. Neurosci. Grad. Training Program, Aurora, CO; [2]Cell and Developmental Biol., [3]Pharmacol., Univ. of Colorado, Anschutz Med. Campus, Aurora, CO

**Abstract:** Oligodendrocytes produce myelin, a lipid rich membrane that wraps neuronal axons in the central nervous system to provide them with metabolic and trophic support and allow for faster action potential propagation. Developmental myelination requires precise spatial and temporal regulation that likely involves communication between oligodendrocytes and neurons, and it is essential for normal nervous system function. In the mature brain, neuronal activity promotes oligodendrocyte progenitor cell (OPC) proliferation, differentiation, and myelination. To test how neuronal activity modulates OPC differentiation in the early developing brain, we used designer receptors exclusively activated by designer drugs (DREADDs) to chemogenetically inhibit or increase activity in post-mitotic Nex-expressing cortical neurons in young mouse pups. Activation of inhibitory Gi-DREADD by clozapine N-oxide (CNO) in mice from P2-P8 resulted in reduced cFos expression in DREADD-expressing Nex neurons, suggesting a reduction of neuronal activity. Unexpectedly, our preliminary data suggest that chemogenetic decrease of neuronal activity in the cortex during this period caused OPCs to differentiate prematurely in both the corpus callosum and the cortex. Here we identify gene expression changes in these cells in response to reduced neuronal activity. Further, we investigate the molecular mechanisms governing this premature OPC differentiation as well as

the timing of the impact of increased or decreased neuronal activity on oligodendrocyte maturation.

**Disclosures:** **T. Allen:** None. **K. Given:** None. **W. Oh:** None. **W.B. Macklin:** None.

**Poster**

**PSTR010. Oligodendrocyte Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR010.06/D24

**Topic:** B.09. Glial Mechanisms

**Support:** NSF1456818
NIH NS118731
NIH MH116003
NE Stem Cell grant

**Title:** Glutamate delta-1 receptor regulates oligodendrocyte progenitor cell differentiation and myelination in normal and demyelinating conditions

**Authors: *S. GAKARE**, J. BHATT, K. NARASIMHAN, S. DRAVID;
Dept. of Pharmacol. and Neurosci., Creighton Univ., Omaha, NE

**Abstract:** Abstract: Oligodendrocyte progenitor cells (OPCs) are the only glial cells to form synapses. Signaling at axo-OPC synapses promotes remyelination by OPCs. The glutamate delta 1 receptor (GluD1) belongs to the delta family of ionotropic glutamate receptors, but it does not function as a conventional ligand-gated ion channel. Instead, GluD1 is critical for formation and/or maintenance of glutamatergic synapses. The potential role of GluD1 in OPC regulation has not been explored. In this study, we investigated the role of GluD1 in OPC-mediated myelination during basal (development) and pathophysiological (cuprizone-induced demyelination) settings. Initially, we sought to determine the expression pattern of GluD1 in OPCs and found a significant colocalization of GluD1 puncta with neuron-glial antigen 2 (NG2, a OPC marker) in the motor cortex as well as in dorsal striatum. Importantly, we found that the ablation of GluD1 leads to an increase in the number of myelin-associated glycoprotein (MAG+) cells i.e., mature OLs in the corpus callosum and motor cortex at P40 without affecting the number of NG2+ OPCs in these regions, indicating that the loss of GluD1 selectively facilitates the differentiation of OPCs into OLs but not the proliferation of OPCs. Further, deletion of GluD1 enhanced myelination in the corpus callosum and motor cortex, as indicated by increased myelin basic protein (MBP) staining at P40, suggesting that GluD1 may play an essential role in the developmental regulation of myelination during the critical window period. On the contrary, in cuprizone-induced demyelination, we observed reduced MBP staining in the corpus callosum of GluD1 KO mice. Furthermore, cuprizone-fed GluD1 KO mice showed more robust behavioral motor deficits including shorter latency to fall in rotarod test and hypolocomotion in open field

test. Collectively, our results demonstrates that GluD1 plays a critical role in OPC regulation and myelination in normal and demyelinating conditions.

**Disclosures:** **S. Gakare:** None. **J. Bhatt:** None. **K. Narasimhan:** None. **S. Dravid:** None.

**Poster**

**PSTR010. Oligodendrocyte Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR010.07/D25

**Topic:** B.09. Glial Mechanisms

**Support:** R01 AA024774
R25 GM086264
NSF GFRP 1938059
UMass Spaudling Smith Fellowship
UMass IALS Midigrant
UMass CNS Seed-Bridge Fund

**Title:** Tracking new myelin formation during adolescence and across the lifespan

**Authors:** C. DE ANDA GAMBOA[1], A. FLORES BONILLA[2], D. A. KELLY[3], S. AKLI[4], J. F. BERGAN[3], ***H. RICHARDSON**[5];
[1]UMass PREP, [2]Neurosci. and Behavior Program, [3]Psychological and Brain Sci., [4]Univ. of Massachusetts, Amherst, MA; [5]Univ. of Massachusetts Amherst, Amherst, MA

**Abstract:** In periods of rapid growth and development, myelin-producing glial cells (oligodendrocytes, OLs) wrap lipid-rich myelin segments around axons, supporting fast communication across different regions of the brain. White matter increases in frontotemporal brain regions during adolescence and this corresponds with improvements in executive functioning, complex cognitive processing, and stress regulation. These functions are impacted early in degenerative diseases like Frontotemporal Dementia and Alzheimer's Disease, suggesting the integrity of white matter tracts interconnecting these regions may be impaired. It is therefore important to better understand the cellular dynamics of OLs during adolescence and the temporal and spatial patterns of new myelin formation during this critical developmental period. A major challenge in the field has been visualizing and tracking *de novo* myelin sheath formation. Herein we have successfully distinguished between new and previously formed myelin using a double transgenic conditional mouse reporter line (NG2-CreERt: Tau-mGFP). By combining this approach with double/triple immunofluorescent labeling and confocal imaging, we have discovered that there is rapid differentiation of OLs and formation of new myelin throughout frontotemporal white matter regions including the forceps minor of the corpus callosum, the anterior commissure, as well as white matter tracts of the hippocampus and amygdala. Using CLARITY and light sheet microscopy we generated a 3D map of myelinated tracts that were formed during adolescence and remain in these frontotemporal regions well into

adulthood at 6 months of age. The cellular dynamics of OLs may change across the lifespan and affect myelin maintenance and the function of these frontotemporal circuits, leaving these pathways susceptible to degeneration. These findings could have significant implications for identifying targets and timelines of therapeutic intervention as individuals age.

**Disclosures: C. De Anda Gamboa:** None. **A. Flores Bonilla:** None. **D.A. Kelly:** None. **S. Akli:** None. **J.F. Bergan:** None. **H. Richardson:** None.

**Poster**

**PSTR010. Oligodendrocyte Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR010.08/D26

**Topic:** B.09. Glial Mechanisms

**Title:** Myelin lipid synthesis modulates neural activity and is essential for motor learning

**Authors: *Y. AOYAMA**[1], D. KATO[1,2], K. NISHIDA[3], Y. TAKAHASHI[4], T. SAKAMOTO[4], I. TAKEDA[1,2], T. TATEMATSU[1], S. GO[1], Y. SAITO[1], S. KUNISHIMA[1], J. CHENG[1], H. LINGNAN[1], Y. TACHIBANA[3], S. SUGIO[1], R. KONDO[1], F. ETO[4,5], S. SATO[4], A. MOORHOUSE[6], I. YAO[4,5], K. KADOMATSU[1], M. SETOU[4], H. WAKE[1,2];
[1]Nagoya Univ., Nagoya, Aichi, Japan; [2]Natl. Inst. of Natural Sci., Okazaki, Japan; [3]Kobe Univ., Kobe, Japan; [4]Hamamatsu Univ., Hamamatsu, Japan; [5]Kwansei Gakuin Univ., Sanda, Japan; [6]UNSW Sydney, Sydney, Australia

**Abstract:** Lipids are one of the major components of myelin and contribute to the insulation of action potentials of nearby axons. These myelinated axons form white matter and act as cables to propagate information to distinct brain regions (Nave, 2010). Human MRI studies show that learning and training, such as playing the piano and juggling, lead to structural changes in white matter (Sampaio-Baptista and Johansen-Berg, 2017; Scholz et al., 2009). In mice, MRI studies have also found similar structural changes associated with increased expression of myelin-related proteins (Sampaio-Baptista et al., 2013).Impaired regulation of myelin related protein caused myelin dis-regulation resulted in motor learning deficits (Kato et al., 2020). Accumulated evidence suggested that motor learning requires activity-dependent myelination and regulation of temporal pattern of the neural activity which is essential for effective learning process. However, it is unclear whether lipid synthesis changes during motor learning and if so, whether this change contribute to neural populational activity regulation that required for motor learning. Here, we conducted in vivo two-photon imaging to quantify lipid synthesis changes during a lever-pull task in the primary motor cortex (M1). Three motor learning phases were examined: early, middle, and late. Increased movement-related calcium activity amplitudes correlated positively with both early and late lever-related neural activity. Next, to identify if myelin specific lipids are altered in response to changes in the neural circuitry associated with motor learning. We performed MALDI-IMS and LC-MS/MS of the M1 for mice in each phase of motor learning process, and quantified levels of different sphingomyelin (SM), galactosylceramide (GalCer) and

sulfatide. We showed that the SM are associated with the increase in task-related neural activity during early stage of learning, while the increase in GalCer is associated with synchrony of neural activity during the late stage. As GalCer is synthesized from SM via the galactosyltransferase (CGT) enzyme, we further evaluate its role in triggering or maintaining motor learning neural synchrony by oligodendrocyte (OLs) specific CGT inhibition using adeno associate virus induced short-hairpin RNA (shRNA). Finally, inhibition of GalCer synthesis via OLs specific CGT shRNAi resulted in motor learning impairment. These results suggest that the myelin lipid synthesis is regulated in a neural activity-dependent during motor learning. This study will be the key to understanding the mechanisms in neurodegenerative diseases related to altered lipid synthesis.

**Disclosures:** **Y. Aoyama:** None. **D. Kato:** None. **K. Nishida:** None. **Y. Takahashi:** None. **T. Sakamoto:** None. **I. Takeda:** None. **T. Tatematsu:** None. **S. Go:** None. **Y. Saito:** None. **S. Kunishima:** None. **J. Cheng:** None. **H. Lingnan:** None. **Y. Tachibana:** None. **S. Sugio:** None. **R. Kondo:** None. **F. Eto:** None. **S. Sato:** None. **A. Moorhouse:** None. **I. Yao:** None. **K. Kadomatsu:** None. **M. Setou:** None. **H. Wake:** None.

**Poster**

**PSTR010. Oligodendrocyte Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

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**Topic:** B.09. Glial Mechanisms

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Regenerative Medicine Minnesota
NCAA Postgraduate Scholarship

**Title:** Par1 limits cholesterol and lipid biosynthesis in myelin development and regeneration

**Authors: *L. WURTZ**[1], H. YOON[2], E. TRIPLET[3], C. CHOI[2], W. SIMON[2], I. A. SCARISBRICK[2];
[2]Physical Med. & Rehabilitation, Rehabil. Med. Res. Ctr., [3]Neurol., [1]Mayo Clin., Rochester, MN

**Abstract:** Myelin is a specialized, cholesterol-dependent membrane that facilitates neuronal communication. Loss of myelin in inflammatory demyelinating conditions such as multiple sclerosis has been linked to local cholesterol biosynthesis disruptions. This suggests that pathogenic cues may curtail cholesterol production and, conversely, blocking these pathways may be therapeutic. We previously demonstrated that Protease Activated Receptor 1 (PAR1) knockout mice show accelerated myelin development and increases in myelin regeneration

across models of demyelinating disease. In this study, we identify that the improvements in myelin production observed in PAR1 knockouts are linked to increases in key regulators of cholesterol and lipid biosynthesis. Using bulk RNA sequencing of the spinal cord from P120 adult mice (n=4 PAR+/+ and PAR1-/-; female), we find that PAR1 knockouts show increased expression (>Log2-FC; FDR<0.05) of the requisite transcripts needed for de novo cholesterol biosynthesis, including Hmgcs1 and Sqle. Targeted quantitative PCR from the spinal cord of mice at the peak of myelination (P21), and in early adulthood (P45) (n=3-4/group; male/female) confirmed increases ($p<0.05$; One Way ANOVA) in Hmgcs1 in PAR1-/- mice compared to PAR+/+ controls. Biological pathway analysis of the differentially expressed genes between PAR1+/+ and PAR1-/- reveals cholesterol biosynthesis, axon ensheathment, and lipid biosynthesis as the most significantly enriched gene sets. Next, we modeled the impact of PAR1 deletion in acute focal demyelination (lysophosphatidylcholine injection in ventral spinal cord white matter; n=5-8; male; P70) or chronic demyelination (cuprizone feeding for 6 wk + 4 wk recovery; n=4-5; male; P70). When challenged with remyelination, Olig2+ PAR1-/- oligodendrocytes had greater expression of master regulators of lipid and cholesterol biosynthesis, SREBP1 and SREBP2, compared to wild type mice. In turn, PAR1-/- oligodendrocytes also showed increases in HMGCS1, a key enzyme in the cholesterol biosynthesis pathway. Finally, using GC-MS and LC-MS, we report the differences in total, free, and esterified cholesterol, and in several lipid species in the whole spinal cord and in the myelin enriched fraction between PAR1+/+ and PAR1-/- mice (n=3-5; female; P21 and P60). These results underscore the importance of PAR1 in modulating key factors involved in cholesterol and lipid biosynthesis in myelin producing cells developmentally and during remyelination in the adult CNS. Further work targeting this receptor may prove important in restoring cholesterol and lipid homeostasis to restore myelin in neurological injury and disease.

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**Poster**

**PSTR010. Oligodendrocyte Mechanisms**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR010.10/D28

**Topic:** B.09. Glial Mechanisms

**Support:** NIH intramural grant no. ZIAHD000713

**Title:** Oligodendroglia in learning and memory

**Authors: *M. MUNYESHYAKA**[1,2], R. FIELDS[3];
[1]NIH, Natl. Inst. of Mental Hlth. (NIMH), Bethesda, MD; [2]Mol. Med., Cleveland Clin. Lerner Col. of Med., Cleveland, OH; [3]NIH, The Eunice Kennedy Shriver Natl. Inst. of Child Hlth. and Human Develop. (NICHD), Bethesda, MD

**Abstract:** Synaptic plasticity is considered the primary neural mechanism underlying learning and memory, but recent research reveals that myelin-forming glia, oligodendroglia, are involved in many forms of learning. As a result, there have been several reviews on activity-dependent myelination, which are redundant and targeted to researchers in the myelin biology field. Our synthesis provides a fresh viewpoint to consider cellular mechanisms of oligodendroglia in learning and memory but from the reference frame of memory researchers, not myelin researchers. We integrate such new findings into the established conceptual framework and nomenclature used by neuroscientists and psychologists in the field of learning and memory. We show how oligodendroglia and their progenitor cells are involved in information acquisition, storage, and retrieval, including their involvement in short-term and long-term memory. In addition to participating in implicit memory, procedural, spatial, and fear memory, current evidence suggests the involvement of oligodendroglia in declarative memory, working memory, and the influences of attention, emotion, neuronal excitability, and sleep on memory. Oligodendroglia contribute to learning by responding to experience-driven changes in neural impulse activity to optimize the speed of impulse conduction in neural circuits through modifications of myelin and by influencing synaptogenesis and synaptic function. Participation of oligodendroglia expands beyond the classical synaptic plasticity to system-wide network function where precise spike time arrival, coherence, and neural oscillations synchrony are essential for information processing, storage, and retrieval. By integrating the role of oligodendroglia and their progenitors into the larger literature of learning and memory, we illuminate the contribution of oligodendroglia in ways synaptic plasticity alone cannot accomplish and provide answers to long-standing questions in the field of learning while raising new questions to help bridge the gap between the two areas of research.

**Disclosures: M. Munyeshyaka:** None. **R. Fields:** None.

**Poster**

**PSTR010. Oligodendrocyte Mechanisms**

**Location:** WCC Halls A-C

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**Topic:** B.09. Glial Mechanisms

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Spaulding Smith Fellowship
NIH NIAAA R01AA024774
IALS Midigrant
CNS Seed-Bridge

**Title:** Determine how adolescent alcohol drinking alters corticotropin releasing factor (CRF) and axonal myelination in the central amygdala in adulthood in male and female mice

**Authors: *A. FLORES BONILLA**[1], S. AKLI[2], R. SENTHIKUMAR[2], B. DE OLIVEIRA[2], A. RAJVANSHI[2], N. AMIRA[2], H. N. RICHARDSON[3];
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**Abstract:** Neural circuits involved in regulating stress responses undergo maturational processes during adolescence including myelination of axons, and new myelin formation may also be an adaptive and experience-driven process. Indeed, early life adversity leads to higher functional connectivity between the prefrontal cortex and central amygdala (CeA) later in adulthood, which is accompanied by heightened corticotropin releasing factor (CRF) stress peptide in this region. Alternatively, chronic alcohol exposure reduces myelin and oligodendrocyte gene expression and CRF peptide levels in the CeA, but these effects may rebound following removal of alcohol. The goal of the current study was to test the following hypotheses: 1) new myelin is added to CeA axons following a history of adolescent alcohol drinking, and 2) a proportion of these myelinated axons contain CRF peptide. We used our inducible transgenic mouse reporter line (NG2CreERt: Tau-mGFP) to tag and track oligodendrocytes forming new myelin in the CeA following adolescent binge drinking. Adolescent male and female mice were exposed to 20% v/v alcohol or water (n=9-11 per group) starting at postnatal day 28 using a modified drinking in the dark (DID) paradigm for 2 weeks. Cumulatively, mice consumed an average of 38.66 g/kg of alcohol with an average of 4.16 g/kg/4h per session. Following 2 months of abstinence, mice were intracardially perfused, and brains were extracted and sectioned. Immunohistochemistry was used to fluorescently co-label GFP ("new myelin") and CRF. Our results indicate that myelinated axons coming into or going out from the CeA is colocalized with CRF peptide expression. Further analyses will determine if a history of alcohol exposure during adolescence followed by long-term abstinence is sufficient to induce increase myelination of these CeA axons, which could lead to changes in stress responsivity.

**Disclosures: A. Flores Bonilla:** None. **S. Akli:** None. **R. Senthikumar:** None. **B. De Oliveira:** None. **A. Rajvanshi:** None. **N. Amira:** None. **H.N. Richardson:** None.

**Poster**

**PSTR010. Oligodendrocyte Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR010.12/D30

**Topic:** B.09. Glial Mechanisms

**Title:** A protective role of Schwann cells for the integrity of microvasculature in human skin

**Authors: *M. TSUTSUMI**, A. KIKUCHI, M. YANO, C. SUTTINONT, K. KAJIYA;
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**Abstract:** Peripheral nerves are highly vascularized tissues because of their high metabolic demands and often run parallel to blood vessels (BVs) in the body. Schwann cells (SCs) are peripheral neuronal glia that protect nerve fibers and play a crucial role in neuronal support as well as axon regeneration associated with BVs during peripheral nerve injury. In light of their ability for repair functions and potential clinical applications, cutaneous SCs are attracting attention since the skin is an easily accessible tissue and a rich source of SCs. Yet, the involvement of SCs in skin homeostasis has not been clarified although the importance of sensory afferent fiber innervation is recognized as crucial for skin homeostasis. In this study, we aimed to clarify the morphological features and distribution of SCs in human skin to determine the function of sensory innervation to skin homeostasis focusing on the association of SCs and the microvasculature. First, we observed the morphology of SCs with nerve fibers and BVs in skin specimens from humans at various ages. Immunohistochemical staining was performed by labeling p75NTR for SCs, CD31 for BVs and PGP9.5 for nerve fibers. In the subepidermal area, thin and densely localized branching of SCs near capillary loops and thicker SCs along with BVs were observed, and those decreased with age. During our study, we noticed that BVs lost nerve fiber innervation with age, which may imply that the lack of innervation results in the loss of BVs. To investigate the involvement of sensory innervation to cutaneous BVs, we used a humanized skin model in which iPS-derived sensory neurons sprouted into human skin explants. We found that not only PGP9.5-positive nerve fibers were increased but also p75NTR-positive cells surrounding the newly sprouted nerve fibers, indicating that nerve fiber sprouting integrated with the resident SCs in skin explants. Moreover, the nerve sprouting skin model showed that the CD31-positive structure and NG2-positive pericyte coverage of BVs was maintained. These results suggest that reconstructed glio-neural complexes are involved in the maintenance of BVs in skin organ culture. Finally, permeability assays for Human Umbilical Vein Endothelial Cells (HUVECs) were conducted using monolayer cultures. IL-1β was used for barrier disruption to assess the effects of SCs on the vascular permeability of HUVECs. The conditioned medium showed protective effects on the IL-1β barrier disruption. Our results reveal the detailed cutaneous SC morphology and distribution in human skin during aging. In addition, we demonstrate the role of SCs to maintain the BV structure/integrity and contribute to skin homeostasis.

**Disclosures:** **M. Tsutsumi:** A. Employment/Salary (full or part-time); Shiseido Co., Ltd. **A. Kikuchi:** A. Employment/Salary (full or part-time); Shiseido Co., Ltd. **M. Yano:** A. Employment/Salary (full or part-time); Shiseido Co., Ltd. **C. Suttinont:** A. Employment/Salary (full or part-time); Shiseido Co., Ltd. **K. Kajiya:** A. Employment/Salary (full or part-time); Shiseido Co., Ltd.

**Poster**

**PSTR010. Oligodendrocyte Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR010.13/D31

**Topic:** B.09. Glial Mechanisms

**Support:** GSS suport

**Title:** Oligodendrocyte dynamics during short-term cuprizone treatment.

**Authors: *M. OSO**[1], H. LEE[2], J. MCDONOUGH[2], R. CLEMENTS[3];
[1]Biomed. Sci., [2]Kent State Univ., Kent, OH; [3]Kent State Univ., kent, OH

**Abstract:** The cuprizone animal model is widely used to study toxic demyelination and subsequent remyelination in the central nervous system. Cuprizone, a copper chelator, is therefore frequently used to model multiple sclerosis as well as other demyelinating and degenerative diseases. Studies have shown that acute demyelination in the cuprizone model occurs around 5-6 weeks in various brain regions (corpus callosum and cortex). Our previous work indicates that cuprizone causes permeability in the blood-brain barrier as early as 3 days, with subsequent microglial and astrocyte activation before demyelination. Recent studies suggest that it only takes the first 3 weeks of Cuprizone exposure to cause demyelination at 6 weeks. In the present study, we aim to understand the dynamics of oligodendrocytes and oligodendrocyte progenitor cells (OPCs) during Cuprizone treatment at early time points (3 days, 1 week, and 3 weeks) prior to overt demyelination. Mice were treated with 0.3% cuprizone for up to three weeks sacrificed, brains removed and either fixed and sectioned or immediately frozen on dry ice. Immunohistochemistry was utilized to stain fixed brain sections after sacrifice for OPCs, myelin, and mature oligodendrocytes (OLGs) after 3 days, 1 week, or 3 weeks of cuprizone treatment. The number of cells, the quantity of cell markers, and morphology were quantified. QTR-PCR was used to analyze the gene expression of myelin-associated genes (MOG. MBP. MAG) and PDGFRA. Our results document oligodendrocytes dynamics, and it's gene expression profile during short-term cuprizone treatment compared to control brains.Understanding changes in oligodendrocyte dynamics that precede demyelination is important for developing methods to prevent or reverse neurological impairment.

**Disclosures: M. Oso:** None. **H. Lee:** None. **J. McDonough:** None. **R. Clements:** None.

**Poster**

**PSTR010. Oligodendrocyte Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR010.14/D32

**Topic:** B.09. Glial Mechanisms

**Support:** NIH K12NS098482-06

**Title:** Minimum Effective Dose of Clemastine in a Mouse Model of Preterm White Matter Injury

**Authors: E. ODELL**, N. JABASSINI, A. GREEN, J. R. CHAN, *B. E. L. OSTREM;
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**Abstract:** White matter injury (WMI) is the most common type of brain injury in preterm infants (babies born at less than 37 weeks of completed gestation). Preterm WMI has no effective treatments, and is associated with adverse neurological outcomes, including motor and cognitive disability and seizures. Oligodendrocytes (OLs) and their precursors (oligodendrocyte precursor cells, OPCs) comprise the major cell types implicated in preterm WMI, which involves an arrest of differentiation of OPCs and a reduction in mature OLs and myelin formation. Thus, the OL lineage is an ideal target for therapeutics aimed at promoting recovery after preterm WMI. Clemastine is a first-generation antihistamine previously shown to promote OL differentiation, myelination and motor recovery in animal models of preterm WMI. Clemastine is an excellent candidate treatment for preterm WMI, but the minimum effective dose that promotes neonatal brain repair is unknown. Identification of the minimum effective dose would allow for determination of the target exposure and target plasma levels in future clinical trials in human neonates. Here, we tested 4 doses of clemastine to determine the minimum effective dose in a chronic hypoxia model of preterm WMI. Male and female C57BL/6 mice aged P3 to P10 (equivalent to human gestation weeks 23-40) were exposed to 10% oxygen for 1 week, mimicking a known risk factor for WMI in human neonates. This model recapitulates the histopathological features and adverse motor outcomes of human preterm WMI. We found that mice treated with clemastine at 7.5 mg/kg/day and above had significantly increased mature (CC1+) OLs compared to vehicle-treated animals ($p<0.01$, n=10-26 mice/condition). Mice treated with clemastine at 7.5 mg/kg/day and above also displayed significantly increased myelin (myelin basic protein [MBP] intensity) staining as compared to vehicle-treated animals ($p<0.05$, n=10-26 mice/condition). CC1+ OLs and MBP intensity did not differ significantly between mice reared in normal oxygen and hypoxia-exposed animals treated at a clemastine dose of 7.5 mg/kg/day and above. Lower doses were not effective at promoting myelination after chronic hypoxia. These results establish the lowest effective dose of clemastine in a mouse model of preterm WMI, and pave the way for future clinical trials of this medication in neonates.

**Disclosures: E. Odell:** None. **N. Jabassini:** None. **A. Green:** None. **J.R. Chan:** None. **B.E.L. Ostrem:** None.

**Poster**

**PSTR010. Oligodendrocyte Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR010.15/D33

**Topic:** B.09. Glial Mechanisms

**Title:** Vagus Nerve Stimulation (VNS) drives precise myelin repair and functional improvement following demyelination

**Authors: *R. HUANG**, E. G. HUGHES, C. WELLE;
Univ. of Colorado Anschutz Med. Campus, AURORA, CO

**Abstract:** Multiple Sclerosis (MS) is an inflammatory, demyelinating disorder that damages oligodendrocytes, resulting in myelin loss and eventual axonal degeneration. While demyelination occurs throughout the central nervous system (CNS), increasing evidence suggests that gray matter demyelination is directly correlated with impaired cognitive and motor dysfunction. Current disease modifying therapies mitigate the frequency of demyelinating events, but are not thought to promote lesion repair potentially leading to cumulative damage and functional impairments. There is an unmet need to develop innovative therapeutic approaches that focus on restoration of function through remyelination. Vagus nerve stimulation (VNS) drives neuronal activity and plasticity, leading to functional recovery from neuronal injury in stroke, tinnitus and traumatic brain injury. However, whether VNS can be utilized to drive myelin repair and plasticity remains unexplored. We applied chronic VNS to mice following cuprizone-mediated demyelination and used longitudinal two-photon in vivo imaging to examine the loss and regeneration of oligodendrocytes and myelin in primary forelimb motor cortex over time. We found that VNS enhances the generation of new oligodendrocytes. Moreover, when paired with successful reach outcomes, VNS modulates myelin sheath replacement, enhancing the restoration of the original myelin pattern. Importantly, paired VNS drives long-term motor functional improvement that correlates with the degree of myelin pattern restoration. Together, these findings highlight the beneficial impact of VNS on myelin repair and motor function recovery following demyelination, supporting its potential as a therapeutic approach for demyelinating diseases.

**Disclosures: R. Huang:** None. **E.G. Hughes:** None. **C. Welle:** None.

**Poster**

**PSTR010. Oligodendrocyte Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR010.16/D34

**Topic:** B.09. Glial Mechanisms

**Support:** SenNet Consortium TDA (UG3CA275669)
NIH Grant (R00AG058798)

**Title:** Exploring senescent signatures of oligodendrocyte precursor cells in the aged mouse brain

**Authors: *P. GOMEZ**[1], C. M. CARVER[1], X. ZHANG[1], M. J. SCHAFER[1,2,3];
[1]Robert and Arlene Kogod Ctr. on Aging, [2]Biomed. Engin. and Physiol., [3]Neurol., Mayo Clin., Rochester, MN

**Abstract:** Senescent glia and neurons that accumulate in the aged brain are associated with neurological dysfunction. However, the molecular identities of senescent brain cells and their regional heterogeneity in aging remain poorly understood. We and others previously discovered that myeloid and oligodendrocyte progenitor cell (OPC) subpopulations in the aged brain harbor canonical senescence markers. Due to the dynamic roles of OPCs in brain homeostasis,

discovery of senescent identities may illuminate mechanisms of impairment in the aged nervous system. Here, we investigated whether OPC subpopulations assume senescent cell fates in the aged brain. We cross-referenced published single-cell RNA-sequencing (scRNAseq) datasets of the aged mouse brain to verify that OPCs constitute a significant senescent cell population based on canonical and candidate marker expression. Then, we analyzed OPC identities in aged white matter regions through RT-PCR, immunofluorescent (IF) imaging and imaging mass cytometry (IMC). Analysis of scRNAseq data showed an age-dependent increase in the cell number and percentage of *Cdkn2a*+ (p16+) OPCs. Ingenuity pathway analysis of differentially expressed genes in this OPC cluster revealed an activation of senescence-associated pathways. From the same transcriptomic data, we identified age-upregulated, OPC-specific candidate senescence markers and found an upregulation of these factors in aged versus young white matter via RT-PCR. IF imaging demonstrated an age-associated decrease in the number and density of PDGFRa+ OPCs in the fimbria of the hippocampus. Aged OPCs were also found in close proximity to IBA1+ microglia, whereas young OPCs were more distant. Transgenic clearance of p16-expressing cells in old *p16-INK-ATTAC* mice did not rescue the density change but shifted the interaction profile of old OPCs and microglia towards the young profile. Using IMC, we observed colocalization of senescence markers with aged OPCs. Overall, these studies describe region-defined characteristics of aged OPCs and contribute to emerging knowledge of glial interactions in brain microenvironments. Continued integration of high dimensional data will enable comprehensive mapping of OPC fates in the aged mouse brain. Future experiments will also describe the functional consequences of these age-associated changes to inform regenerative strategies targeting OPCs. FUNDING: SenNet Consortium TDA (UG3CA275669) and R00AG058798

**Disclosures: P. Gomez:** None. **C.M. Carver:** None. **X. Zhang:** None. **M.J. Schafer:** None.

**Poster**

**PSTR010. Oligodendrocyte Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR010.17/D35

**Topic:** B.09. Glial Mechanisms

**Support:** FOREST program (grant number JPNJFR2145）

**Title:** Contribution of oligodendrocyte impairment to cognitive decline with aging

**Authors: *S. KUNISHIMA**[1], D. KATO[1,2], J. CHENG[1], H. WAKE[1,2];
[1]Dept. of Anat. and Mol. Cell Biol., Nagoya Univ. Grad. Sch. of Med., Nagoya/Aichi, Japan; [2]Div. of Multicellular Circuit Dynamics, Natl. Inst. for Physiological Sciences, Natl. Inst. of Natural Sci., Okazaki, Japan

**Abstract:** The white matter is composed of myelinated axons, which act as cables connecting different brain regions. Clinically, elderly people and Alzheimer's disease (AD) patients with

white matter lesions showed significant impaired cognitive function. Furthermore, abnormalities in molecular expression specific to oligodendrocytes (OLs) and their progenitor cells (OPCs) have been reported in AD pathology, suggesting the pathological association between white matter abnormalities with impaired cognitive function. However, the detailed causality of OLs and myelin impairment with cognitive decline is unknown. Here, we aimed to clarify the dynamic and functional response of OLs/OPCs in aging and AD model mice to elucidate the functional pathological mechanism for OLs/OPCs to show cognitive decline. We first investigated functional responses of OLs/OPCs in the white matter of 2-month-old wild type mice (2M WT) and 6-month-old AD model mice (6M AD) with *in vivo* $Ca^{2+}$ imaging using two-photon microscopy. We found that the intensity and latency of $Ca^{2+}$ activity was increased in 6M AD mice compared to 2M WT mice. In addition, $Ca^{2+}$ activity of OLs/OPCs in 6M AD mice increased during the motor learning but not associated with learning process. It is unclear whether these changes in activity are not normal compared to WT, but these results lead us to consider why learning efficiency was declining despite the increase in $Ca^{2+}$ activity of OLs/OPCs. To answer this question, we observed the morphology of the OLs/OPCs in 2M WT, 6M WT, and 6M AD mice. We quantified the process domains of OPCs and found that were reduced in aging and AD pathology. We then measured the number of OLs/OPCs and changes in expression levels of myelin related protein by immune-histochemistry and protein quantification. The number of OPCs decreased, while the number of OLs increased in aging and AD pathology. Furthermore, the expression of myelin basic protein was increased due to the increased number of OL, suggesting promotion of the myelin sheath repairment. In fact, the ultrastructure of the myelin sheath analyzed by electron microscope showed that the repair of the myelin sheath was impaired in 6M AD. These results suggest that, in aging and AD, altered $Ca^{2+}$ activity of OLs/OPCs occurs to induce myelin sheath repairment, resulting in learning deficit. We anticipate that these experiments will provide new insights into the mechanisms of cognitive decline in aging and AD pathology and identify potential therapeutic targets for the future.

**Disclosures:** **S. Kunishima:** None. **D. Kato:** None. **J. Cheng:** None. **H. Wake:** None.

**Poster**

**PSTR010. Oligodendrocyte Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR010.18/D37

**Topic:** B.09. Glial Mechanisms

**Support:** NRF-2019R1A5A202645
NRF-2021R1F1A1061819
HR21C1003

**Title:** Primary Oligodendrocyte Culture: Optimal Procedure and Media Compositions

**Authors: K. HAN KI**[1], *K. BUM JUN[2], S. KOH[3], J. CHOI[4];
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**Abstract:** Oligodendrocytes (OL) are the myelin-forming cells of the central nervous system (CNS), facilitating fast neuronal signal transmission by enabling saltatory conduction, as well as providing metabolic support to the neurons they enwrap. Numerous efforts have been and are being made to study the physiologic and pathologic characteristics of OLs, and a large proportion of this research has been done in vitro, with rodent primary OLs. In this study, we present a new method of primary OL culture, which is a compilation of existing new and old methods for oligodendrocyte progenitor cell (OPC) isolation, along with suggestions for optimal media compositions for the proliferation and differentiation of isolated OPCs and OLs. For OPC isolation, cerebral cortices of postnatal day 1 rats were dissected and dissociated, and the cell suspension was passed through two sequential steps of density centrifugation in 12% and 6% Optiprep$^{TM}$ (Iodixanol), which yield approximately 1-2*10$^{6}$cells/brain. Colonies composed of OPCs (90-95%) and neurons (2-3%) were observed after 5 days of proliferation, and comparison of OPC proliferation media compositions revealed that DMEM/F12 + 2%B27 + 1% GlutaMAX + 20ng/mL PDGF + 10ng/mL FGF + 10ng/mL EGF produced the best results, a two fold increase in viable cell number measured by the WST-8 assay compared to other DMEM or DMEM/F12 based formulas and a 10-fold higher cell number compared to Neurobasal based formulas. After passaging and redistribution, OPCs were proliferated for and additional 2 days for stabilization, in the optimal OPC proliferation media without EGF due to its property to hinder uniform spatial distribution. Differentiation of OPCs to OLs was performed, and branching MBP+ processes were visible in 45-50% of the cells at day 2 of differentiation which further developed into web-like sheets of myelin by day 4. Comparison of OL differentiation media compositions showed that Neurobasal + 2% B27 + 1% N2 + 1% GlutaMAX + 40ng/mL Triiodothyronine (T3) produced the most morphologically complex OLs as analyzed by the Sholl analysis. We lastly confirmed the capacity of OLs obtained through our revamped culture procedure to enwrap neurons and aligned nanofibers. In summary, we present an optimized method for primary OL culture, improving efficiency of the procedure. We observed robust proliferation and differentiation of cells, alongside their capability to myelinate structures, which is the core function of OLs. We also provide suggestions for optimal media formulations at each stage of the culture/cells for desired results, which are applicable to OLs obtained through different isolation methods.

**Disclosures:** **K. Han Ki:** None. **K. Bum Jun:** None. **S. Koh:** None. **J. Choi:** None.

**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.01/D38

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

**Support:** GR128837

**Title:** The E3 Ubiquitin Ligase IDOL Regulates Microglial Phagocytosis in Alzheimer's Disease

**Authors: *S. KAYE**[1], J. ATKINSON[2], J. GAO[3];
[2]The Ohio State Univ. Wexner Med. Ctr., [1]The Ohio State Univ., Columbus, OH; [3]Ohio State Univ., Ohio State Univ., Columbus, OH

**Abstract:** Alzheimer's Disease (AD) is a chronic neurodegenerative disease characterized by the accumulation of disease associated microglia (DAM) surrounding amyloid beta (Aβ) plaques. Previously, we discovered a novel E3 ubiquitin ligase IDOL that serves as a major post-transcriptional regulator of three brain ApoE receptors in the low-density lipoprotein receptor (LDLR) family. We showed that both genetic deletion and pharmacological inhibition of IDOL led to a reduction in the number and size of Aβ plaques and increased expression of genes associated with DAM phenotype. Here we show acute knockdown of IDOL increases microglial phagocytosis of Aβ plaques and the expression of DAM markers, including ApoE and TREM2. Additionally, long-term inhibition of IDOL reduced the number and size of Aβ plaques, decreased plaque-associated neuritic dystrophy, and improved cognitive function in human APP knock-in mice. Furthermore, RNA sequencing data shows that LDLR expression is increased in phagocytic microglia following knockdown of IDOL. These findings suggest that inhibition of IDOL may serve as a potential therapeutic strategy to delay of the progression of Alzheimer's disease.

**Disclosures: S. Kaye:** None. **J. Atkinson:** None. **J. Gao:** None.

**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.02/D39

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

**Title:** Role of adenosine A2A receptor in the olfactory system & implications in Alzheimer's disease pathology

**Authors: *X. AILIYA**, L. BAO, X. XIJIRI, S. KAKUTA, E. EERDUNFU;
Univ. of Tokyo, Tokyo, Japan

**Abstract:** Alzheimer's disease (AD) is the most common dementia. Two types of proteins are usually involved in the disease, amyloid beta (Aβ) and Tau protein. Amyloid-beta precursor protein (APP) express in many tissues and concentrated in the synapses of neurons; its processing could lead to the accumulation of Aβ. One of the earliest regions affected by AD is the olfactory system. However, the role of the olfactory system in AD pathophysiology has remained elusive. This study investigated the relationship between the adenosine A2A receptor (A2AR), the olfactory system, and AD pathology. A2AR modulates synaptic transmission and

neuroinflammation by regulating neuron and glial cells. The OB mediates olfaction via A2AR neurons in mice. The olfactory impairment will appear before AD symptoms. Our studies have shown that the abnormal expression of A2AR appeared before the App accumulation in the olfactory bulb of AD mice. We further examined the olfactory bulb and striatum expression patterns of A2AR by immunostaining and western blotting of AD and WT mice. Data showed that the A2AR expression in AD model mice was higher than in WT mice. The western blotting results showed that A2AR expression became higher age-dependently when there were no significant changes in WT mice. In addition, we used caffeine and adenosine as antagonist and agonist of A2AR in the SH-SY5Y cell line and primary neurons extracted from WT and AD mice. Results showed that the blockade of A2AR using caffeine could maintain the morphology of cells when the adenosine could contribute to the morphology changes in the cells. The RT-PCR results showed that the different concentrations of caffeine would regulate the A2AR expression. The further co-staining of A2AR and Amyloid β-Protein $_{1\text{-}42}$(A$\beta_{1\text{-}42}$) showed that A$\beta_{1\text{-}42}$ accumulated near the cells overexpressing A2AR in OB and striatum in AD model mice but not in WT mice. It will somehow be related to A$\beta_{1\text{-}42}$ formation, and the pathology needs further study. In conclusion, our results showed that the A2AR regulation to the Aβ is similar in the olfactory system and brain. The A2AR dysregulation in the olfactory system appeared earlier than in the striatum, and the timely detection of this abnormality could be a new therapeutic target for AD.

**Disclosures: X. Ailiya:** None. **L. Bao:** None. **X. Xijiri:** None. **S. Kakuta:** None. **E. Eerdunfu:** None.

**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.03/D40

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

**Support:** National Institute of Aging (NIH R01 AG070873-01A1)
NIH/NIAAA (No. R44 75N94019C00010)
New Jersey Commission on Brain Injury Research

**Title:** Inhibition of phosphodiesterase 2 protects neurons against mild traumatic brain injury and Aβ42 oligomers insults

**Authors: *J. GAO**, S. METKAR, Y. XU;
Anesthesiol., Rutgers, The State Univ. of New Jersey, Newark, NJ

**Abstract:** Background: The previous study found that inhibition of Phosphodiesterase 2 ameliorates cognitive impairment in Aβ1-42 oligomers (AβOs) treated mice through antioxidant and antiapoptotic pathway. However, whether PDE2 inhibition produces neuroprotective effects against neuronal damage induced by mild traumatic brain injury (mTBI) in Aβo treated neuronal

and glial cells remains unclear.
Methods: HT-22 cells co-cultured with Aβo-exposed BV2 cells were preteated with PDE2 inhibitor Bay 60-7550 (0.5 μM) for 30 min. The cells were subsequently subject to mild cell-based TBI (m-CTBI) by cell injury controller 30 min after they were exposed to AβOs at 0.5 μM. The cell death was determined by lactate dehydrogenase (LDH) assay 24 h after m-CTBI. The levels of cAMP, cGMP and cytokines such as NF-κB and IL-1β were also detected.
Results: The results suggested that m-CTBI induced AβOs-treated BV2 cells lesion, which caused co-cultured HT-22 cells death as evidenced by increased LDH value in HT-22 cells. However, pretreated BV2 cells with PDE2A inhibitor Bay 60-7550 protected HT-22 cells against m-CTBI plus low dose of AβOs' insults. While treated co-cultured cells with either 0.5 μM AβOs or m-CTBI did not cause HT-22 cells lesion. The further results showed that the expression of NF-κB and IL-1β was increased in AβOs-treated co-cultured HT-22 cells after m-CTBI. However, these effects were rescued by pretreatment with Bay 60-7550. PKA or PKG inhibitor H89 or KT5823 prevented this protective effect, suggesting the involvement of cAMP/cGMP signaling in the effect of Bay 60-7550.
Conclusion: These results provide proof-of-principle for the effectiveness of PDE2A inhibition on modulation of neuronal inflammation and death with TBI-induced AD progression.
Key words: Traumatic brain injury; phosphodiesterase 2A; Alzheimer's disease; LDH assay; neuroinflammation

**Disclosures:** **J. Gao:** None. **S. Metkar:** None. **Y. Xu:** None.

**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.04/D41

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

**Support:** R01 AG079193

**Title:** Infection of olfactory epithelium with alphaherpesvirus elicits cellular remodeling and expression of β amyloid

**Authors: *C. S. NIEMEYER**[1], A. N. BUBAK[2], B. D. BAXTER[3], A. GENTILE-POLESE[3], V. RAMAKRISHNAN[5], P. J. DEMPSEY[4], M. A. NAGEL[2], D. RESTREPO[6];
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**Abstract:** Multiple studies implicate herpes simplex virus type-1 (HSV-1) as initiators or accelerators of Alzheimer's disease (AD) because they increase dementia risk and elicit the same pathological characteristics seen in AD, including amyloid accumulation, neuroinflammation,

neurodegeneration, and cognitive impairment. In a parallel body of literature, early AD is characterized by smell loss, amyloid deposition in the olfactory epithelium (OE), and olfactory sensory neuron (OSN) dysfunction. Previous experiments found the differential gene and protein expression in the olfactory bulb (OB) and olfactory tract (OT) of familial AD (FAD) individuals carrying the autosomal dominant presenilin 1 E280A paisa mutation and age-matched controls. In FAD samples, RNA sequencing showed a transcription profile consistent with (1) viral infection in the OB; (2) inflammation in the OT that carries information via entorhinal cortex from the OB to hippocampus, a brain region essential for learning and memory; and (3) decreased oligodendrocyte deconvolved transcripts, indicating dysregulation of myelination. In order to understand the consequence of viral infection on olfactory epithelial function, we infected undifferentiated human olfactory epithelium cell cultures with HSV-1 (MOI=0.00001, McKrae strain). We found that HSV-1 productively infects the olfactory epithelial cultures by increasing HSV-1 DNA. Using immunofluorescence, we found that acute HSV-1 infection elicited a large increase in the expression of β amyloid and cyclic nucleotide-gated channel subunit 2 (CNGA2, a marker of mature olfactory sensory neurons). These findings raise the possibility that viral infection may disrupt olfactory and downstream hippocampal functions, contributing to the acceleration of FAD progression.

**Disclosures: C.S. Niemeyer:** None. **A.N. Bubak:** None. **B.D. Baxter:** None. **A. Gentile-Polese:** None. **V. Ramakrishnan:** None. **P.J. Dempsey:** None. **M.A. Nagel:** None. **D. Restrepo:** None.

**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.05/D42

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

**Support:** New Jersey TBI grant

**Title:** Inhibition of PDE10 ameliorates cognitive deficits in Alzheimer’s disease by regulation of neuroinflammation

**Authors: *Y. YAN**, Y. XU;
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**Abstract: Inhibition of PDE10 ameliorates cognitive deficits in Alzheimer’s disease by regulation of neuroinflammation**Yuqing Yan, PhD, Ying Xu, PhD/MD *
Department of Anesthesiology, Rutgers University, the State University of New Jersey, Newark, NJ 07103
**Background:** Phosphodiesterase10A (PDE10A) is a dual-substrate enzyme that hydrolyzes both cAMP and cGMP. The initial findings showed that PDE10A is highly expressed in the striatum of brain, which led to most of studies focused on psychotic functions and the development of

PDE10A inhibitors for treatment of schizophrenia. Recent studies suggested that high levels of PDE10A co-localize with synaptophysin in pyramidal neurons in the hippocampus, placing it in key position to regulate synaptic transmission and learning and memory. Alzheimer's disease (AD) is an intractable disease characterized by progressive impairment of the cognitive function and accompanied by psychiatric disorders. However, the role of PDE10A in regulation of AD related memory deficits and psychiatric symptoms remains unestablished.
**Method:** The present study investigated the effects of PDE10A inhibition on cognitive deficits associated with depression- and anxiety-like behaviors in APP/PS1 mouse model of AD. Chronic treatment of PDE10A inhibitor MP-10 (6 mg/kg, i.p.) for 3 weeks significantly improved memory impairment in Novel object recognition (NOR) and Y-maze tests in 8-month of age APP/PS1 mice. The single cell RNAseq and KEGG analyses were used to further analyze the cell types and related signal
pathways that were responsible for the amelioration of learning and memory disorder in AD mice.
**Result:** The behavioral tests suggested that PDE10A inhibitor MP-10 dose-dependently improved cognitive dysfunction in 8 months of age APP/PS1 mice, as evidenced by increased discrimination index in NOR and decreased escape failure in Y-maze tests. The subsequent single cell RNAseq analysis suggested that 22 cell types in the hippocampus were extracted among 42 cell clusters. Further enrichment of KEGG analysis suggested that the changes in cell types and the signaling pathways in AD mice were closely involved in the imbalance of neuroinflammatory and immunity function. **Conclusion:** These findings demonstrate that inhibition of PDE10 plays an important role in AD mice by regulation of the imbalance in immunity and inflammatory function.
**Key words:** PDE10 inhibitor, MP-10, Alzheimer's disease, neuroinflammation, single cells RNAseq analysis; KEGG analysis.

**Disclosures: Y. Yan:** None. **Y. Xu:** None.

**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.06/D43

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

**Title:** Usp15-mediated mitophagy suppression and its role in amyloid plaque formation in alzheimer's disease

**Authors: *X. XIJIRI**, L. BAO, X. AILIYA, S. KAKUTA, E. EERDUNFU;
Univ. of Tokyo, Tokyo, Japan

**Abstract:** Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the accumulation of amyloid plaques and neurofibrillary tangles in the brain. This study investigates the role of ubiquitin-specific peptidase 15 (USP15) in the development of amyloid

plaque formation by influencing mitophagy in AD. Mitophagy is a selective form of autophagy crucial for maintaining mitochondrial quality control and cellular homeostasis. Recent evidence suggests that USP15, a deubiquitylating enzyme, is highly expressed in the brain and may contribute to the etiology of neurodegenerative disorders. So, enhancing mitophagy has the potential to prevent tau hyperphosphorylation and improve memory in AD models. To investigate the role of USP15 dysregulation and mitochondrial dysfunction in AD, we examined the expression patterns of USP15 in the olfactory bulb and hippocampus, regions more prone to pathological protein aggregation, using immunostaining in AD model mice. Our findings revealed USP15 increased expression in the brains of AD model mice and exhibited co-localization with Ibal and $A\beta_{1-42}$ in an age-dependent manner in AD mouse models compared to wild-type mice. Additionally, expression of USP15 is decreasing with aging, which provide the potential of being a biomarker in preclinical stage of AD. *In vitro* experiments utilizing SH-SY5Ycells treated with urolithin A (UA) showed decreased expression of $A\beta_{1-42}$ and USP15.These results suggest that enhancing mitophagy may lead to reduced $A\beta_{1-42}$ and USP15 expression. Subsequently, RNAi-mediated knockdown of USP15 followed by western blotting demonstrated that the expression of LC3B and $A\beta_{1-42}$ was ameliorated, confirming that deregulation of USP15 expression can rescue the over-expression of $A\beta_{1-42}$ by enhancing mitophagy. Furthermore, western blotting analysis revealed higher expression of LC3B in AD model mice, indicating deficient mitophagy. Notably, in wild-type mice, USP15 expression increased in the presence of aggregated amyloid β. These findings suggest an interaction between USP15 and $A\beta_{1-42}$ in AD, leading to dysregulation of mitophagy through the induction of LC3B. In conclusion, USP15 plays a critical role in the development of amyloid plaques in AD by suppressing mitophagy. Dysregulation of USP15-mediated mitophagy impairment results in increasing $A\beta_{1-42}$ production, ultimately contributing to the pathogenesis of AD. Further investigations are warranted to validate USP15 as a potential therapeutic target for AD treatment.

**Disclosures:** **X. Xijiri:** None. **L. Bao:** None. **X. Ailiya:** None. **S. Kakuta:** None. **E. Eerdunfu:** None.

**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.07/D44

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

**Support:** NIH Grant 2RF1NS074256-11

**Title:** C-x-c motif chemokine ligand 14 enhances microglial function in vitro - implications for Alzheimer's disease

**Authors: *J. PATHOULAS**, J. ZHOU, R. YAN;
Neurosci., Univ. of Connecticut Sch. of Med., Farmington, CT

**Abstract:** Alzheimer's disease (AD) is the most common cause of dementia worldwide and currently lacks disease-modifying therapies. Abnormal accumulation of extracellular amyloid beta (Aβ) leads to a cascade of neuropathological changes resulting in gliosis, impaired synaptic function, neuroinflammation, and neuronal death. Previous work has shown that astrocyte-specific knockout (KO) of beta-secretase 1 (BACE1), the enzyme responsible for generation of Aβ, significantly reduced Aβ pathology in a mouse model of AD. Analysis of differentially expressed genes from single-cell transcriptomic studies on BACE1 KO astrocytes revealed a significant upregulation of C-X-C motif chemokine ligand 14 (CXCL14). CXCL14 is a secreted chemoattractant protein for peripheral immune cells such as monocytes and neutrophils. Interestingly, genome-wide association studies have identified several single nucleotide polymorphisms near the CXCL14 gene locus associated with increased risk of AD pathology. However, the role of CXCL14 in AD and its effect on glial cell function are unknown. A previous report demonstrated that CXCL14 stimulated phagocytosis in peripheral monocytes suggesting CXCL14 may enhance phagocytosis in other immune cell types. Here, we investigate the effect of CXCL14 on microglial function and phagocytosis *in vitro*. Chamber slides were plated with 1 x $10^4$ BV2 immortalized microglia overnight and then pretreated with 100 ng/mL human recombinant CXCL14 or PBS for 2 hours. Next, green pHrodo e. coli bioparticles were added to each chamber at a final concentration of 100 ug/mL for 1 hour. Cells were then fixed with 4% paraformaldehyde, counterstained with phalloidin, mounted and cover slipped. Using confocal microscopy, 10 images (~250 cells) per sample were obtained and analyzed using ImageJ software quantifying mean raw internal density of bioparticle signal per cell. Sample means were then averaged per condition. Our results demonstrate that CXCL14 significantly increased uptake of pHrodo bioparticles in treated cells compared to control ($p = 0.002$, student T-test, $n = 3$). This data suggests that CXCL14 enhances BV2 microglial phagocytosis *in vitro* making it a potential target for modulating microglial phagocytosis of Aβ in AD. Additionally, we outline the development of a novel tetracycline-controlled transactivator CXCL14 overexpression mouse line. We will cross this overexpression mouse line with the 5xFAD mouse line to test the effect of CXCL14 on alleviating AD-related memory deficits and AD pathology *in vivo*. These studies could help identify CXCL14 as a novel therapeutic target for AD.

**Disclosures:** **J. Pathoulas:** None. **J. Zhou:** None. **R. Yan:** None.

**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.08/D45

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

**Support:** Fixel Institute for Neurological Diseases
McKnight Brain Institute
NIH

**Title:** Assessing changes in peripheral immune cell function caused by the PLCG2 P522R genetic variant

**Authors: *H. STALEY**[1], J. JERNIGAN[2], K. B. MENEES[2], N. NEIGHBARGER[2], C. COLE[2], M. G. TANSEY[2];
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**Abstract:** Alzheimer's disease (AD) is the most common neurodegenerative disease affecting our aging population, and it is characterized by the presence of beta-amyloid plaques extracellularly, and the formation of tau tangles within neurons. Current research focuses on the extent and manner in which these two pathological hallmarks compromise neuronal health. However, further evidence has implicated the immune system as another contributing factor to neurodegenerative disease progression. The brain itself contains various immune cells, of particular note are microglia, which function to maintain homeostasis within the brain as well as contribute to neuronal health. Genetic variants expressed primarily in microglia have been shown to have both negative and positive effects on risk for developing AD, further emphasizing the importance of this subset of cells on neuronal health. Specifically, a protective genetic variant in the phospholipase C gamma 2 (PLCG2) gene of microglia was recently discovered in a small cohort of AD cases. This genetic mutation, P522R, affords protection from AD-related cognitive decline even in the presence of beta-amyloid plaques. Recent evidence has shown that microglia with this mutation show an increase in both phagocytosis and inflammatory cytokine secretion. Although PLCG2 is highly expressed in brain-resident microglia, it is also expressed at lower levels in peripheral immune cells, including monocytes, B-cells, and natural killer cells. However, whether the P522R mutation has any effect on these cell types has been largely overlooked. For this reason, we investigated whether peripheral immune cells carrying this mutation may also show functional differences. We performed a whole blood stimulation assay to determine the inflammatory phenotype of blood resident immune cells, as well as flow cytometry on splenocytes, peripheral blood mononuclear cells, and the brains of P522R variant carrier mice. We determined that mice that carry the P522R mutation have a different peripheral inflammatory phenotype upon stimulation, as well as changes in peripheral cell populations. Based on this we concluded that peripheral immune cells that carry the P522R mutation do have altered function compared to wild type peripheral immune cells. Additionally, this altered function could suggest that those that carry this mutation may also display a protective immune phenotype outside of the brain.

**Disclosures: H. Staley:** None. **J. Jernigan:** None. **K.B. Menees:** None. **N. Neighbarger:** None. **C. Cole:** None. **M.G. Tansey:** None.

**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.09/D46

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

**Support:** SJBSM Competitive Research Pilot Project Program YIN-2020

**Title:** Angiotensin II Stimulates p-Tau and Microglia Cell Inflammatory Responses

**Authors: *J. GARCIA**[1], Y. RODRIGUEZ[2], S. CASTAÑO-PESANTE[1], F. J. RODRIGUEZ-MATOS[1], Y. INOSTROZA-NIEVES[1];
[1]Biochem. and Pharmacol., San Juan Bautista Sch. of Med., Caguas, PR; [2]Biomed. Sci., Univ. Interamericana de Puerto Rico, San Juan, PR

**Abstract:** Alzheimer's Disease (AD) is the most common cause of dementia. AD patients had increased extracellular amyloid β plaques and intracellular hyperphosphorylated tau (p-tau) in neurons. Recent studies have shown an association between the Renin-Angiotensin System (RAS) and AD. The involvement of RAS has been mediated through Angiotensin II (AngII), which is overexpressed in aging brains. However, the exact mechanism of how AngII contributes to AD is unknown. Thus, we hypothesize that AngII increases brain inflammation activating NF-kB pathway and ROS generation. In the human cortical neuron cell line, HCN2, treatment with AngII increased p-tau, and the AT1R antagonist, Losartan, blocked this effect. In addition, the effects of AngII were studied in human microglial cells (HMC3), resident innate immune cells of the central nervous system (CNS). In HMC3 cells, treatment with AngII upregulated the gene expression of IL-6 (3.9 folds ± 1.2, $p<0.01$, n=4) and increased IL-6 concentrations by 83% ($p<0.05$, n=4), as measured by ELISA. The changes in IL-6 were blocked by the AT1R antagonist, Losartan. Also, AngII induced the production of TNF-α, increasing its concentration by 90% ($p<0.05$, n=4), an increase that was also blocked by Losartan. To study a possible mechanism, we used the NF-κB (p65) Transcription Factor Assay Kit and found that AngII increased NF-kB transcriptional activity by 64% ($p<0.05$, n=4) compared to the control, and this effect was blocked by Losartan. We then quantified Nitric Oxide (NO) production and reactive oxygen species (ROS) production by using Griess Reagent and MUSE Oxidative Stress assay, respectively. In these cells, NO and ROS production was significantly increased by AngII ($p<0.05$, n=4), and treatment with Losartan blunted their production ($p<0.05$, n=4). In addition, AngII treatment induced iNOS overexpression (2.5 folds ±0.8, $p<0.05$, n=4). These results suggest that AngII can activate microglial cell pro-inflammatory responses through NF-kB pathway and increased ROS production, which may contribute to the pathophysiology of CNS inflammation and AD.

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**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.10/D47

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

**Support:** NIH Grant RF1AG063540
NIH Grant R01AG073918
Ellison Foundation
Weill Neurohub

**Title:** Hipsc-derived microglia challenged with disease-relevant stimuli assume multiple transcriptomic phenotypes similar to alzheimer's disease

**Authors: *A. COCHOIT**[1], A. REID[4], S. MAMDE[5], J. E. YOUNG[2], K. PRATER[3], S. JAYADEV[1];
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**Abstract:** Microglia are the resident innate immune cells of the brain. Microglia survey, phagocytize and prune neuronal synapses during healthy brain development and maintenance. This supportive role of microglia becomes disrupted during the progression of Alzheimer's disease (AD), a neurodegenerative disorder characterized pathologically by the presence of amyloid beta (abeta) plaques and phosphorylated tau tangles. To better understand the functional changes microglia undergo in AD, we had previously profiled microglia from control and AD brain, with single nuclei RNA sequencing and discovered a diversity of microglial AD associated phenotypes. Here we aimed to model microglial diversity in vitro for the purpose of hypothesis testing using human induced pluripotent stem cell derived microglia (iMGs). We exposed iMGS to three conditions: 1) vehicle 2) 1uM abeta, and 3) 1uM etoposide for 24 hours followed by single cell RNA sequencing. Etoposide causes DNA damage and was chosen to model the accumulated DNA damage in AD and aging. After QC, our dataset contained over 75,000 microglia. The microglia grouped into twelve transcriptionally distinct clusters. This highlighted the heterogeneity of microglia in vitro in addition to the known heterogeneity in vivo. We then utilized gene set enrichment analysis (GSEA) to determine biological pathways that correlate to the gene expression for each cluster. We found that abeta treatment led to an increased proportion of two clusters, "cluster 2" and "cluster 11" compared to control and etoposide treatment. Cluster 2 was defined by enrichment of cell cycle genes and pathways. Cluster 11 showed an upregulation of TREM2 and APOE, two AD risk genes implicated in AD pathogenesis. Cluster 11 was enriched for endolysosomal pathways, regulation of plasma lipoprotein, interferon signaling and amyloid beta clearance similar to the AD associated cluster we find in human AD brain. Validation experiments will include protein expression immunocytochemistry to detect highly expressed genes specific to these different subpopulations. Our data highlight the diversity of microglia phenotypes even in vitro and suggest both that hiPSC are a good model of microglia and can assist in the identification of mechanistic biology behind cellular responses to AD pathology.

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**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.11/D48

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

**Support:** NIH Grant RF1AG063540
Weill Neurohub
Ellison Foundation
NIH Grant R01AG073918

**Title:** Leveraging an hiPSC derived neuron-microglia co-culture model of Alzheimer's disease-associated microglia subpopulations to investigate non-cell autonomous mechanisms of neurodegeneration

**Authors: *A. N. REID**[1], A. COCHOIT[2], K. E. PRATER[2], C. KINOSHITA[1], A. PARIHAR[2], J. YOUNG[1,3], S. JAYADEV[2];
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**Abstract:** Compelling evidence from genome wide association studies and human brain transcriptomics implicate non-neuronal cell contribution to Alzheimer's disease (AD) pathology and progression. Microglia, the innate immune cells of the brain, take on multiple distinct transcriptomic and morphological phenotypes associated with AD pathology. However, it remains unclear how each distinct AD-associated microglia subpopulation contributes to neurodegeneration. A recent single-nucleus RNAsequencing analysis of microglia isolated from the brains of individuals with AD and age-matched controls revealed a subpopulation of microglia significantly increased in AD brains and distinguished by upregulated expression of cytosolic DNA/RNA recognition genes. Here, we investigate the mechanisms driving cytosolic accumulation of nucleic acids in this subset of microglia using a co-culture of human induced pluripotent stem cell (hiPSC) derived microglia and neurons. To distinguish between soluble and insoluble factors driving nucleic acid accumulation, we cultured microglia with a) healthy neurons, b) neurons exposed to UV damage, and c) healthy neurons in conditioned media from UV injured neurons. For all three co-culture conditions we assessed morphology and cytosolic double stranded DNA (dsDNA) using immunocytochemistry (ICC), and transcriptomic profile via single-cell RNAsequencing (scRNAseq) of CViA2 wild type (WT) microglia and CViA2 EOFAD PSEN2 heterozygous mutant (HET) microglia following one week of co-culture with neurons. Analysis of ICC revealed that under control conditions microglia-neuron co-cultures exhibited no dsDNA accumulation and took on highly ramified morphology. When cultured in the presence of UV-injured neurons, regardless of genotype, microglia became smaller and less ramified, and significant cytosolic dsDNA accumulation was observed. Furthermore, while morphological trends remained consistent, more modest dsDNA accumulation was also observed in both WT and HET microglia cultured with healthy neurons when in UV-conditioned media, suggesting soluble factors also contribute to microglial nucleic acid accumulation. We are now assessing these three microglia-neuron co-culture conditions using scRNAseq to determine how soluble and non-cell autonomous factors can influence microglial transcriptomic diversity and the regulation of distinct biological pathways. Together, these findings exhibit the utility of *in*

*vitro* hiPSC derived co-cultures in modeling AD-associated microglia subpopulations in order to gain insight into therapeutically relevant microglial mechanisms contributing to AD pathology.

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**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.12/D49

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Human Microglial State Dynamics in Alzheimer's Disease Progression.

**Authors: *A. NI SCANNAIL**[1], N. SUN[1], M. VICTOR[1], X. XIONG[1], N. LEARY[1], S. PROSPER[1], S. VISWANATHAN[2], X. LUNA[1], C. BOIX[1], B. JAMES[1], Y. TANIGAWA[1], K. GALANI[1], H. MATHYS[3], X. JIANG[1], A. NG[1], D. BENNETT[4], L.-H. TSAI[1], M. KELLIS[1]; [1]MIT, Cambridge, MA; [2]Univ. of Maryland, Baltimore, MD; [3]Univ. of Pittsburg, Pittsburg, PA; [4]Rush Univ. Med. Ctr., Chicago, IL

**Abstract:** In response to changes to the brain microenvironment, microglia undergo vast rearrangements in transcriptional programs to alter its functional repertoire and cellular state. Altered microglial states are thought to mediate neuroinflammation and exacerbate neurodegeneration. Yet, the spectrum of cellular states adopted by microglia in response to aging or disease are poorly understood. This is in large part due to the low numbers of microglia that have been profiled from postmortem human brains, limiting our understanding of the role of these cells in the pathobiology of neurological diseases. Here, using single-nucleus sequencing (snRNA-seq), we report the transcriptomes of 194,000 microglia isolated from 444 human subjects across six brain regions. Of these individuals, 220 displayed varying degrees of Alzheimer's disease (AD) pathology. Our data reveals the molecular signatures of 12 distinct microglial states, including inflammatory and lipid processing states that were present in significantly increased proportions in AD individuals and positively correlated with levels of amyloid plaque and tau tangle burden. Using transcription factor-driven regulatory networks, we inferred master regulators of microglial state transitions, and defined the regulatory relationship between microglial states. In addition, we demonstrate that forced expression of regulators of microglia homeostasis could induce homeostatic features in microglia-like cells (iMGLs) derived from human induced pluripotent stem cells (iPSCs). Additionally we leveraged iMGLs to recapitulate transcriptional programs that governs microglial response to the phagocytosis of amyloid beta fibrils, uncovering a temporal program of inflammatory microglia state transitions that map to snRNA-seq of aged human brains. Collectively, our study provides a roadmap to design microglia state specific therapies aimed at curbing neuroinflammation and halting Alzheimer's disease progression.

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**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.13/D50

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH Grant 1R21NS094881
NIAID Grant R21 AI148409
NIAID Grant 2R42AI122574

**Title:** The impact of AD on white matter function

**Authors:** *S. BALTAN, **S. ZERIMECH**, H. NGUYEN, H. OFFNER;
OHSU, Portland, OR

**Abstract:** Multiple sclerosis (MS) is a chronic disease with prominent axon dysfunction that affects over 2 million patients globally. Demyelinating lesions and optic neuritis are hallmarks of MS, and current treatments are disease-modulating drugs. The strongest genetic effect in MS has been attributed to the major histocompatibility complex (MHC). Experimental autoimmune encephalomyelitis (EAE) is a commonly used MS mouse model to develop and validate disease-modulating therapies. Previous studies using an EAE model demonstrated that major histocompatibility complex Class II constructs can reverse ongoing clinical signs of severe EAE. These constructs block binding and downstream signaling of macrophage migration inhibitory factors (MIF-1/2) through CD74, thereby inhibiting phosphorylation of extracellular signal-regulated kinase (ERK) activation and tissue inflammation and promoting remyelination. In our study, we directly assessed axon function properties and tested the restorative value of DRhQ using two distinct white matter (WM) tracts, corpus callosum (CC) and optic nerves (MON), in an EAE mouse model. Male C57BL/6 mice (8-12 weeks) were immunized with subcutaneous (s.c) injection of an emulsion of an encephalogenic peptide in complete Freund's adjuvant to induce EAE and were treated with 5 daily s.c. injections of DRhQ or vehicle at onset of clinical signs of EAE for a total of 10 days. On the day of experiments, DRhQ-treated mice had scores of ~1 whereas vehicle treated mice had scores of ~4.5. Evoked extracellular compound action potentials (CAPs) across the CC and MONs were recorded from control, DRhQ and vehicle treated mice. On CC, CAPs displayed a typical 2-peak shape, representing myelinated and unmyelinated conducting axons. On MONs, CAPS displayed a 3-peak shape, representing fast, intermediate, and slow conducting axons. The functional integrity of axons was monitored by quantifying the CAP area. The excitability of axons was tested by evoking CAPs at various stimulation intensities. EAE drastically altered axon conduction characteristics by targeting axon

integrity and damaging myelin correlated with oligodendrocyte loss while leading to microglial and astrocyte activation. These architectural changes also underlined the increased vulnerability to a subsequent ischemic attack. DRhQ administration after the onset of EAE promoted WM integrity and function and reduced subsequent vulnerability to ischemic injury.
We provide direct evidence that DRhQ has "repair" capacity, for it reversed EAE damage in WM, therefore we propose DRhQ as an effective therapeutic with possible clinical application for MS patients.

**Disclosures: S. Baltan:** None. **S. Zerimech:** None. **H. Nguyen:** None. **H. Offner:** None.

**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.14/D51

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

**Support:** Carney Institute Zimmerman Innovation Award in Brain Science
US Dept. of Veterans Affairs N2864-C
NIH Grant R21AG077697
Alzheimer's Association Grant ABA-22-965518

**Title:** A three-dimensional xenograft culture system to study human iPSC-derived microglia in health and Alzheimer's disease

**Authors: *S. BROWN**[1,2,3], A. DREXLER[2,1,3], K. CONNOLLY[1,4], Y.-W. A. HUANG[1,4,5], D. A. BORTON[1,2,3,5,6];
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**Abstract:** Despite decades of research, Alzheimer's disease (AD) remains a severe public health crisis, affecting nearly 6.7 million Americans and accounting for 60-80% of dementia cases worldwide. The confounding and complex nature of possible mechanisms behind AD-associated pathologies has limited the ability to identify successful targets for therapeutic intervention. Growing evidence implicates microglia as a key player in the neuroinflammatory processes that underlie a number of neurodegenerative diseases, including Alzheimer's Disease and AD-related dementia (ADRD). However, extensive in vitro characterization of both primary and stem cell-derived microglia (iMGs) has shown rapidly shifting cell "states", marked by changes in form, function, and gene expression patterns in response to their culture environment. These responses to the ex vivo environment can render cell states that do not mirror those found in vivo, which limits the study of human microglia-specific mechanisms. Interestingly, recent studies demonstrated that xeno-engraftment of cultured human iMGs into rodent brains in vivo can effectively drive cell states that are more similar to microglia found in the human brain. The

success of these xenograft studies suggests that a hybrid system, effectively combining the human microglia genotype (human iPSC-derived cells) with a physiologically relevant microenvironment, is needed to produce human microglia phenotypes appropriate for studying human diseases like AD. Here, we present a hybrid in vitro model combining human iMGs and rodent-derived cortical cells to form a three-dimensional xenograft culture for the study of complex human microglial behaviors in neuroinflammatory mechanisms that underlie AD. GFP-labeled human iMGs are engrafted into primary three-dimensional cortical “microtissues” and monitored in real time via live confocal imaging. Healthy and AD-mutant iMG behaviors are assayed for acute and longitudinal response to neuroinflammatory stimulation. We demonstrate use of an in vitro culture system that uniquely allows us to decipher influences of AD-promoting genetics on microglial functional phenotypes during neuroinflammatory processes thus expanding in vitro techniques to further probe cell-specific influences of microglia in AD.

**Disclosures: S. Brown:** None. **A. Drexler:** None. **K. Connolly:** None. **Y.A. Huang:** None. **D.A. Borton:** None.

**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.15/D52

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

**Support:** AbbVie, Inc.
Alzheimer's Association AARF-9550302678
Alzheimer's Research UK
Cure Alzheimer's Fund
NIH RF1 AG054199
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NIH R01 AG066429
NIH R01 AG072719
NIH R01 AG067763
NIH R21 NS104609

**Title:** Integrated proteomics analysis of cell type-specific extracellular vesicles identified disease-related molecules associated with activated astrocytes in Alzheimer's disease

**Authors: *Y. YOU**[1,2], S. MURAOKA[2], S. A. SHAFFER[3], M. BLURTON-JONES[4], W. W. POON[5], K. BORGMANN[6], S. IKEZU[1,2], T. IKEZU[1,2];
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**Abstract:** Extracellular vesicles (EVs) have emerged as crucial mediators in understanding neurodegenerative diseases, including Alzheimer's disease (AD), due to their ability to transfer pathogenic molecules. Capturing cell type-specific EVs from patient-derived body fluids or biopsies and profiling their contents by transcriptomic or proteomic analyses provide a useful method to study the pathophysiology of AD. However, information on cell type-specific EV proteomic datasets from human samples is still very limited. In this study, we sought to define human CNS cell type-specific EV protein signatures that could be employed for cell type EV isolation and investigate their potential roles in AD pathology. We performed combined label-free and tandem mass tag-labeling based quantitative mass-spectrometry of EVs isolated from human induced pluripotent stem cells (hiPSCs) and AD brain tissues to conduct a comprehensive EV proteomics study on AD. Novel cell type-specific EV protein markers were identified from hiPSC-derived excitatory neurons (e.g., NCAM1, ATP1A3), astrocytes (e.g., LRP1, ITGA6), microglia-like cells (e.g., CD300A, ITGAM) and oligodendrocytes (e.g., LAMP2, FTH1). The weighted protein co-expression network analysis (WGCNA) of brain-derived EV proteomics from 11 healthy controls, 8 mild cognitive impairment (MCI) and 11 AD patients identified a protein module, which were enriched with astrocyte-derived EV (AEV) markers and plasma membrane molecules (e.g., integrins), was most significantly associated with AD pathology and cognitive function. Furthermore, molecular characterization of EVs derived from human primary astrocytes confirmed the upregulation of integrins under inflammatory condition compared to the quiescent condition. Functional studies demonstrated that these integrins-enriched AEVs promoted increased neuronal uptake and negatively impacted neurite differentiation and neuronal firing. Overall, our study presents novel human neural cell type-specific EV markers, highlights the dynamic role of astrocyte-derived EVs in the pathogenesis of AD, and provides a valuable framework for future EV studies on neurodegenerative diseases.

**Disclosures: Y. You:** None. **S. Muraoka:** None. **S.A. Shaffer:** None. **M. Blurton-Jones:** None. **W.W. Poon:** None. **K. Borgmann:** None. **S. Ikezu:** None. **T. Ikezu:** None.

**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.16/D53

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** European Union’s Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 813263

**Title:** Organotypic cortical brain slices from adult rats as an ex-vivo study platform for neurodegenerative diseases

**Authors: *M. N. DABROWSKA**, J. M. MCMAHON, U. FITZGERALD;
Univ. of Galway, Galway, Ireland

**Abstract:** Adult rats, with their fully developed central nervous system (CNS), exhibit similar pathological changes and symptoms as observed in ageing CNS of humans experiencing neurodegenerative conditions. This makes mature rats a superior model for studying neurodegenerative disease compared to neonatal animals. An animal *ex vivo* model, mimicking a human brain sulcus, is the closest representation of the cell's natural 3D orientation, having all types of CNS cells and keeping endogenous signalling pathways intact. However, there is evidence that tissue derived from adult rats demonstrates limited viability in *ex vivo* culture, typically not exceeding a duration of 7 days.
We aimed to obtain an intact interhemispheric fissure from adult rat coronal brain slices that can model a human brain sulcus and determine metabolic activity and survival of fissure-containing slices derived from different anatomical areas.
Sequential coronal slices (300μm) were cultured in Millicell Culture Plate Inserts. Medium enriched with different concentrations of FBS (0-10% FBS) were compared to investigate the effect on viability. Metabolic activity was determined by testing of supernatant with alamarBlue™ reagent every 7 days. Cortical slices were significantly more metabolically active ($p<0.001$, N=4) in media enriched with 10% of FBS compared to groups cultured in reduced FBS concentration. The new approach prolonged the viability of the slices up to 21 days *in vitro*. Results were supported by a viability/cytotoxicity assay. As an acute response to the culture environment, the tissue slices started to swell. Changes in slice area were monitored over time. The first 7 days *in vitro* (DIV) were marked as crucial for the slices' recovery and establishment of a sustainable system. Any further experimental manipulations took place after that period. Caudal slices (~Bregma point -1.33 mm) were significantly more metabolically active ($p<0.05$) than rostral regions.
Our model introduces a distinctive and novel possibility to utilize adult organotypic brain slices as an *ex vivo* research platform for investigating neurodegenerative disease, encompassing drug testing and the analysis of cortical pathology in conditions such as multiple sclerosis. Obtaining the interhemispheric fissure provides the opportunity to mimic human sulci. Furthermore, the variation in metabolic activity along the rostral-caudal axis emphasises the significance of tracking the anatomical origin. This novel information aids in establishing an optimal culture setup for cortex-focused *ex vivo* experiments.

**Disclosures:** **M.N. Dabrowska:** None. **J.M. McMahon:** None. **U. FitzGerald:** None.

**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.17/Web Only

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Dysfunctional Redox Regulation of the NLRP3 Inflammasome and Neurodegenerative Disorders

**Authors: *K. HSIAO**, R. C. DETH, M. G. SABBIR;
Pharmaceut. Sci., Nova Southeastern Univ., Fort Lauderdale, FL

**Abstract:** The aging population is increasing, and the number of Alzheimer's disease (AD) cases is projected to increase dramatically. Recently, studies on neuroinflammation and the role of the nucleotide-binding domain (NOD)-like receptor protein 3 (NLRP3) inflammasome have gained considerable attention, largely due to the COVID-19 pandemic. NLRP3 activation has been associated with aging-related diseases, including AD. Considering that NLRP3 activity is influenced by oxidative stress, we hypothesized that changes in redox status might play a crucial role in the low-grade inflammation associated with aging, known as "inflammaging.". This study aims to investigate how abnormal metabolic activity in antioxidant-related pathways and NLRP3 activation contribute to neuroinflammation in AD. In this study, we used cultured cells (monocytic leukemia cell line THP-1) and postmortem brain tissues to investigate the mechanism by which oxidative conditions stimulate inflammasome activity and to compare their sensitivity to NLRP3 activation, both during priming (i.e., gene expression) and activation (i.e., IL-1β formation) stages. PCR and Western blots analyses were conducted to compare human frontal cortex samples from postmortem cases, aiming to better understand the link between inflammaging and neurodegeneration. An ELISA assay was performed with the THP-1 cells to further identify redox-related pathways that regulate NLRP3-dependent secretion of IL-1β. PCR analysis conducted on postmortem brain tissue from male and female subjects belonging to different age groups (young: 0-16 years, older: 67-80 years, AD: 71-83 years) demonstrated an association between expression of the transsulfuration enzyme cystathionine-β-synthase (CBS) and NLRP3 mRNAs . The expression of NLRP3 in the frontal cortex was significantly higher in older subjects compared to younger ones but significantly lower in AD brains compared to older controls. However, NLRP3 activity, as measured by caspase-cleaved IL-1β, was higher in older control and AD samples compared to young controls. THP-1 cells treated with the protein kinase C (PKC) activator phorbol 12-myristate 13-acetate (PMA) served as a study model for amyloid beta (Aβ) induction of IL-1β secretion. Our study demonstrates that mRNA expression levels of NLRP3 and IL-1β genes are abnormal in postmortem AD brains compared to elderly control subjects, suggesting that aging-related changes contribute to NLRP3 inflammasome activation in AD. However, further studies are required to comprehend the relationship between NLRP3 and oxidative stress in AD.

**Disclosures: K. Hsiao:** None. **R.C. Deth:** None. **M.G. Sabbir:** None.

**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.18/D54

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH R01 AG069232-01A1
Picower Neurological Disorder Research Fund

**Title:** Gamma Sensory Stimulation Alters the Microbiota-Gut-Brain Axis

**Authors: *L. BOZZELLI**[1], D. RODRIGUES AMORIM[1], N. BUIE[2], S. LI[3], L. M. COX[3], R. RAJU[1], L.-H. TSAI[1];
[1]MIT, Cambridge, MA; [2]Massachusetts Eye and Ear, Boston, MA; [3]Brigham and Women's Hosp., Boston, MA

**Abstract:** Gamma entrainment using sensory stimulation (GENUS) has been shown to offer protective effects in multiple mouse models of neurodegeneration. Given the compelling role of the brain-gut microbiome axis in driving neurodegenerative diseases, most of which are strongly associated with aging, we sought to examine whether GENUS could alter the gut microbiome using wildtype aged mice. Here, we report that non-invasive gamma (40Hz) audio and visual sensory stimulation reduced intestinal levels of tissue-resident macrophages and alpha-synuclein—a protein relevant to Parkinson's disease (PD). Analyses via fecal microbiome sequencing and metabolomics revealed significant changes in specific bacterial strains as well as levels of short-chain fatty acids. We next sought to identify whether GENUS could engage brain regions involved in brain-gut axis circuitry; thus, we examined the insular cortex. Notably, we found that GENUS significantly increased levels of insular cFos, while reducing microglia number and markers of microglial activation. Together, these data suggest that gamma stimulation can have far-reaching effects in the periphery, and that these effects may be mediated through insular cortex circuitry projecting to the peripheral organs. Therefore, GENUS may be an effective tool for holistically promoting healthy microbiota-gut-brain function.

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**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.19/D55

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH R01AT011460-01
NIH R37-NS051874-2
2020 BBRF Young Investigator Grant 28961
NIH R01DA029639
NIH R01MH122971
NIH 1R01DA045549
NIH 1R01MH114031
NSF 1848029

**Title:** 40 hz auditory and visual stimulation promotes glymphatic clearance

**Authors:** M. H. MURDOCK[1], ***C.-Y. YANG**[1], N. SUN[1], P.-C. PAO[1], C. BLANCO-DUQUE[1], M. C. KAHN[1], N. S. LAVOIE[1], M. B. VICTOR[1], M. ISLAM[1], F. GALIANA[1], N. LEARY[1], S. WANG[1], A. BUBNYS[1], E. MA[1], L. A. AKAY[1], T. KIM[1], M. A. SNEVE[2], Y. QIAN[2], C. LAI[4], M. M. MCCARTHY[5], N. KOPELL[5], M. KELLIS[2,6], K. D. PIATKEVICH[3,4], E. BOYDEN[2], L.-H. TSAI[1,6];
[1]The Picower Inst. of Learning and Memory, Massachusetts Inst. of Technol., Cambridge, MA; [2]McGovern Inst., [3]Media Lab., MIT, Cambridge, MA; [4]Westlake Inst. for Advanced Study, Hangzhou, China; [5]Dept. of Mathematics and Statistics, Boston Univ., Boston, MA; [6]Broad Inst. of MIT and Harvard, Cambridge, MA

**Abstract:** The glymphatic system promotes brain metabolic waste clearance through the exchange of cerebrospinal fluid (CSF) and interstitial fluid (ISF). Alzheimer's disease (AD) mouse models exhibit impaired glymphatic clearance which is thought to contribute to amyloid and tau accumulation in the brain. In previous studies, we have shown gamma entrainment using sensory stimuli (GENUS) can induce 40 Hz neural activity in multiple brain regions, reduce amyloid burden, and improve performance in tasks involving learning and memory. Here, we sought to test if GENUS can promote amyloid clearance in part through glymphatic routes by using 6-month-old 5xFAD mouse model. First we confirmed GENUS induces a 40 Hz neural response in frontal cortex. 40 Hz auditory and visual stimulation decreased the amyloid burden in medial prefrontal cortex (mPFC). Interestingly, after one hour 40 Hz stimulation, we observed increased CSF tracer accumulation. Glymphatic clearance is known to be mediated by arteriolar vasomotion, which is coupled with neural gamma oscillations. Thus, we measured arterial pulsatility, and observed increased vasomotion from 40 Hz stimulation. Furthermore, 40 Hz stimulation increased amyloid accumulation in cervical lymph nodes, further suggesting glymphatic clearance routes. Together, our results suggest that 40 Hz stimulation can promote amyloid clearance in part through glymphatic routes and likely involves vasomotion.

**Disclosures: M.H. Murdock:** None. **C. Yang:** None. **N. Sun:** None. **P. Pao:** None. **C. Blanco-Duque:** None. **M.C. Kahn:** None. **N.S. Lavoie:** None. **M.B. Victor:** None. **M. Islam:** None. **F. Galiana:** None. **N. Leary:** None. **S. Wang:** None. **A. Bubnys:** None. **E. Ma:** None. **L.A. Akay:** None. **T. Kim:** None. **M.A. Sneve:** None. **Y. Qian:** None. **C. Lai:** None. **M.M. McCarthy:** None. **N. Kopell:** None. **M. Kellis:** None. **K.D. Piatkevich:** None. **E. Boyden:** None. **L. Tsai:** None.

**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.20/D56

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Abca7 loss-of-function variants induce phospholipid disruptions and dna damage in ad patient tissue and ipsc-derived neurons

**Authors: *S. E. WRIGHT**, D. VON MAYDELL, J. BONNER, P.-C. PAO, L.-H. TSAI;
The Picower Insitute for Learning and Memory, MIT, Cambridge, MA

**Abstract:** Loss of function (LoF) variants in ATP binding cassette subfamily A member 7 (ABCA7) increased the risk of developing Alzheimer's disease (AD) by an odds ratio (OR) ~2. The mechanisms by which ABCA7 LoF increases AD risk and the cell types most strongly affected remain unclear. Here, we performed single-nuclear RNA-sequencing of 41 human post-mortem samples from the prefrontal cortex (PFC) of ABCA7 LoF carriers and matched control individuals. We identified perturbed processes related to metabolic, lipid, cell cycle, and synaptic genes across multiple cell types. Excitatory neurons showed profound perturbations in gene clusters indicating mitochondrial dysfunction, DNA repair defects, and reduced lipid biosynthesis. We performed lipidomics in patient PFC and in iPSC-derived neurons to characterize the lipid dysregulation caused by ABCA7 LoF, and find altered levels of numerous phospholipid species, including phosphatidylcholine. This study provides a detailed atlas of ABCA7 LoF in the human brain and suggests that lipid dysregulation in neurons may be the underlying insult by which ABCA7 LoF increases AD risk.

**Disclosures: S.E. Wright:** None. **D. von Maydell:** None. **J. Bonner:** None. **P. Pao:** None. **L. Tsai:** None.

**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.21/D57

**Topic:** B.09. Glial Mechanisms

**Support:** NIA Grant U19AG069701
NIA Grant RF1AG082314
NIA Grant RF1AG082314

**Title:** Vegf-a in serum protects against memory impairment in app/ps1 transgenic mice by blocking neutrophil infiltration

**Authors: *F. QI**, J. ZHENG, L.-J. WU;
Neurol., Mayo Clin., Rochester, MN

**Abstract:** Activation of innate immunity in the brain is a prominent feature of Alzheimer's disease (AD). The present study investigated the regulation of innate immunity by wild-type serum injection in a transgenic AD mouse model. We found that treatment with wild-type mouse serum significantly reduced the number of neutrophils and microglial reactivity in the brains of APP/PS1 mice. Mimicking this effect, neutrophil depletion via Ly6G neutralizing antibodies resulted in improvements in AD brain functions. Serum proteomic analysis identified vascular endothelial growth factor-A (VEGF-A) and chemokine (C-X-C motif) ligand 1 (CXCL1) as factors enriched in serum samples, which are crucial for neutrophil migration and chemotaxis,

leukocyte migration, and cell chemotaxis. Exogenous VEGF-A reversed amyloid β (Aβ)-induced decreases in cyclin-dependent kinase 5 (Cdk5) and increases in CXCL1 in vitro and blocked neutrophil infiltration into the AD brain. Endothelial Cdk5 overexpression conferred an inhibitory effect on CXCL1 and neutrophil infiltration, thereby restoring memory abilities in APP/PS1 mice. Our findings uncover a previously unknown link between blood-derived VEGF signaling and neutrophil infiltration and support targeting endothelial Cdk5 signaling as a potential therapeutic strategy for AD.

**Disclosures:** **F. Qi:** None. **J. Zheng:** None. **L. Wu:** None.

**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.22/D58

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** Harvard Brain Science Initiative - Stephen Van R. Winthrop Fund for ALS Research
New York Stem Cell Foundation

**Title:** Characterization of choroid plexus inflammation in amyotrophic lateral sclerosis (ALS) mouse model

**Authors: *A. DONG**[1,2], S. GELB[2], H. XU[2], A. BURBERRY[3,4], K. EGGAN[3,4,5], M. LEHTINEN[2,6];
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**Abstract:** Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurodegenerative disease for which there are no effective treatments. Motor neuron loss in the brain and spinal cord, a hallmark of ALS, results in muscle atrophy and paralysis. Biomarkers of neuroinflammation, including increased microglial activation, elevated proinflammatory cytokines, and leukocyte infiltration, are commonly found in ALS patients. The choroid plexus, an epithelial-endothelial convolute within brain ventricles that forms the blood-cerebrospinal fluid barrier and houses immune cells, is a known entry point for immune cell infiltration. A recent postmortem study of ALS patients showed choroid plexus barrier damage and macrophage accumulation, suggesting choroid plexus involvement in regulating ALS inflammatory responses. We aim to gain a deeper understanding of choroid plexus inflammation in ALS using a mouse model. The *C9orf72* gene is one of the most frequently mutated genes in ALS. A loss-of-function *C9orf72* knockout (KO) mouse line was created by Drs. Cat Lutz and Robert Baloh to model neuroinflammatory aspects of ALS. We studied choroid plexus

inflammation using this model. Through histological analysis, we recapitulated key findings from human pathology, including choroid plexus immune cell infiltration and barrier inflammation. Samples included multiple litters with both male and female mice, and all quantification methods were conducted blindly. Further, our lab has developed a two-photon live imaging platform to investigate fluorescently labeled cells of the choroid plexus. We studied choroid plexus macrophages in *C9orf72* KO mice and wildtype littermate controls by evaluating their mobility, motility, and trafficking longitudinally and in real time. Our data point towards enhanced immune activation in the choroid plexus of *C9orf72* KO mice. Future studies will investigate the impact of existing and pre-clinical ALS therapeutics on choroid plexus pathology. Collectively, our work sheds light on how systemic neuroinflammation in ALS may disrupt choroid plexus structure and function, ultimately helping to guide the development of novel ALS treatments targeting neuroinflammation.

**Disclosures: A. Dong:** None. **S. Gelb:** None. **H. Xu:** None. **A. Burberry:** None. **K. Eggan:** None. **M. Lehtinen:** None.

**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.23/D59

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** R01AA025591
T32AA007471

**Title:** Prior alcohol exposure does not potentiate alcohol-induced neurodegeneration after a long period of abstinence

**Authors: *S. A. COLLINS**, K. NIXON;
Col. of Pharm. - Div. of Pharmacol. & Toxicology, The Univ. of Texas at Austin, Austin, TX

**Abstract:** Excessive alcohol consumption, a characteristic of alcohol use disorder (AUD), is known to result in neurodegeneration and neuroimmune activation. Given the chronic and relapsing nature of AUD, individuals are at a high risk of incurring further damage with subsequent drinking. Our lab has previously demonstrated that a four-day exposure to ethanol not only induces neurodegeneration but can shift microglia into a primed state. Primed microglia may cause a sensitized pro-inflammatory reaction and subsequent damage when re-exposed to ethanol. Whether priming persists long-term sufficient to potentiate damage is not known. Therefore, adult male and female Sprague-Dawley rats were administered two cycles of four-day binge ethanol exposure separated by 28 days. During both binges, rats were gavaged with either ethanol diet (25% w/v) or an isocaloric control diet in vanilla Ensure Plus® every 8 hours for 4 days. The dose of ethanol administered was determined by intoxication behavior which produced a mean dose of 9.4±0.4 g/kg/day in the first binge and a similar 8.9±0.4 g/kg/day in the second

binge. These doses resulted in similar mean blood ethanol concentrations (BECs) of 461.1±30.3 mg/dL and 456.8±12.0 mg/dL respectively. Following the last dose of ethanol, animals were monitored for withdrawal severity using a 4-point scale for 17 hours. Withdrawal behavior averaged 1.2±0.2 in the first binge and 0.9±0.1 in the second binge which were both equivalent to hyperactivity, and peaked (maximum score) at 3.2±0.2 and 3.2±0.1 respectively which were both equivalent to head tremors. Rats were then sacrificed two days later via transcardial perfusion, and brains were removed, post-fixed, and sectioned in a 12 series of 40µm sections. Brains were stained with FluoroJade B (FJB), a marker for neurodegeneration, and FJB+ cells were quantified under blue light excitation (fluorescent microscopy). When compared to control animals, a one-way ANOVA revealed a significant increase in FJB+ cells in piriform cortex ($p<0.001$; $p<0.0001$), posterolateral cortical amygdala ($p<0.001$; $p<0.001$) perirhinal/entorhinal cortex ($p<0.001$; $p<0.001$), and the hippocampal dentate gyrus ($p<0.0001$; $p<0.0001$) of both single and double binge rats (respectively). However, the extent of neurodegeneration in the double binge rats was comparable to a single binge exposure. Thus, these data suggest that microglia priming is likely to resolve after a long period of abstinence.
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**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.24/D60

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH/NEIHS R01 ES027245
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NIH/NEIHS R01 ES034196

**Title:** Aberrant Subcellular Dysregulation of Epitranscriptomic Writer METTL3 in Environmentally Linked Synulceinopathy Model of Parkinsonism

**Authors: *D. C. J. MILLER**[1], A. EALY[2], H. JIN[2], V. ANANTHARAM[2], A. KANTHASAMY[2], A. G. KANTHASAMY[2];
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**Abstract:** Parkinson's disease (PD), dementia with Lewy bodies (DLB) and other synucleinopathies associated with Alzheimer's-related dementia (ADRD) are characterized by the accumulation and release of abnormal aggregates of misfolded α-synuclein (αSyn) from neurons. Compelling evidence reveals that misfolded αSyn triggers chronic neuroinflammation, marked by a vicious cycle of prolonged microglial activation, and an upregulation of inflammasome and other related neuroinflammatory cytokines and chemokines. Interactions

between environmental factors and PD pathogenic gene defects are key to understanding disease pathogenesis. In this regard, we recently demonstrated that the environmental neurotoxic Parkinsonian metal manganese (Mn) interacts with αSyn to induce protein aggregation and the subsequent proinflammatory inflammasome signaling cascade in microglial cells. However, the precise upstream molecular mechanisms governing the activation of microglia by Mn-induced αSyn aggregation remain enigmatic. Since m6A epitranscriptomic mRNA modification represents a major top-tier regulator of mRNA cellular dynamics, we investigated the possible role of m6A epitranscriptomic mRNA modifications in Mn-αSyn-induced neuroinflammation. Herein, we show that METTL3, the main catalytic component of the m6A methyltransferase complex, is robustly upregulated in the Mn-exposed C20 human-derived microglial cell model. Our analysis of nuclear and cytoplasmic localization reveals that METTL3, canonically considered a nuclear protein, was more highly abundant in the cytoplasm compared to nuclear expression following Mn insult. Immunofluorescence analysis further demonstrates that METTL3 was positively correlated with activated caspase-3 in response to Mn and aggregated αSyn. Moreover, analysis of the global m6A modification level showed direct correlation with METTL3 expression following Mn treatment, further suggesting METTL3 to be a key epitranscriptomic modulator of Mn-αSyn-induced neuroinflammation. Collectively, our data suggest that Mn upregulates overall METTL3 expression, induces its subcellular mislocalization, contributes to caspase-3 activation, and leads to aberrant changes in global m6A modifications of RNA in microglial cells. Future studies will explore the functional significance of the observed METTL3 upregulation and subcellular translocation in relation to the neuroinflammatory processes stimulated by Mn. Overall, our data demonstrate that the m6A writer METTL3 may be a major regulator of environmental factor-induced chronic inflammation in synucleinopathies.

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**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.25/D61

**Topic:** B.09. Glial Mechanisms

**Support:** R01NS120331

**Title:** Proteomic and transcriptomic analyses of synaptosome preparations from C9orf72 Frontotemporal Dementia iPSC Neurons

**Authors: *A. M. SPILLMAN**[1,2], R. G. SATTLER[1];
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**Abstract:** An important aspect of neuronal function and communication in the central nervous system is the maintenance and refinement of synaptic networks through the selective pruning of synapses, which occurs predominantly, but not exclusively, during development. Interestingly, these processes are also triggered in neurodegenerative diseases and are thought to be responsible for the observed loss of synapses in these disorders, which include Alzheimer's Disease, Frontotemporal Dementia, and other related dementias. Astrocytes and microglia are known to contribute to synaptic pruning during development and thereby play an important role in activity-dependent synapse remodeling. Numerous pathways have been implicated in this process, including the activation of the complement cascade, which is proposed to prime the synapses for removal by exposing so-called 'eat me' signals onto neuronal synapses. Here, we sought to uncover "eat me", but also 'spare me' signals deposited onto neuronal synapses in *C9orf72* Frontotemporal Dementia (FTD) using patient-derived induced pluripotent stem cells (iPSC) differentiated into cortical neurons. To study proteins at the synaptic level, a series of centrifuge-based fractionations were performed to obtain a synaptosome preparation where the final fraction is enriched in synaptic proteins. These synaptosome preparations will be generated from neuronal monocultures as well as neuron-glia (astrocytes and/or microglia) co-cultures and compared between disease and healthy control. We will investigate candidate protein expression, including protein members of the complement cascade pathway, via standard western blot analysis. In addition, we will perform unbiased protein and local mRNA analyses via proteomics and transcriptomic assessments, respectively. Proposed synapse loss will be assessed in sister cultures via measurements of neuronal firing and quantification of synapse density via fluorescent immunostaining of pre-and postsynaptic marker proteins. Candidate synaptic proteins will be assessed mechanistically through genetic and/or pharmacological (including blocking antibodies) manipulations in the iPSC models.

**Disclosures: A.M. Spillman:** None. **R.G. Sattler:** None.

**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.26/D62

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NINDS Grant 1R01NS114656

**Title:** [18F]ROStrace PET as a biomarker of mitochondria-induced neuroinflammation in prodromal Parkinson's disease

**Authors:** Y. ZHU[1], A. YOUNG[2], N. KOHLI[1], C.-J. HSIEH[2], M. SHELDON[1], J. CONI[1], S. LI[2], H. LEE[2], D. WALLACE[1], R. MACH[2], ***M. J. MCMANUS**[1];
[1]Children's Hosp. of Philadelphia, Philadelphia, PA; [2]Radiology, Univ. of Pennsylvania, Philadelphia, PA

**Abstract:** Parkinson's disease (PD) most commonly affects patients late in life, but it is estimated that the neurodegenerative processes begin decades earlier than the diagnostic symptoms. Mitochondrial dysfunction appears an early and persistent mediator of PD pathology. Genetic and environmental PD-risk factors impinge on mitochondrial function, resulting in the release of mito-stress signals, such as reactive oxygen species (ROS). ROS and other mitochondrial stress signals are immunogenic, directly activating resident immune cells of the brain. The activated immune cells then produce more ROS, which ultimately leads to neurotoxicity. Therefore, we hypothesized that if we could noninvasively track ROS, this mito-immune stress signal could serve as a biomarker for PD pathogenesis. We developed a positron emissions tomography (PET) ligand, [18F]ROStrace, that crosses the BBB and is selectively retained in the brain after the tracer is oxidized by superoxide or related ROS (1). [18F]ROStrace retention was quantified using dynamic 60min PET/CT acquisitions over the course of PD-like progression in 2 mouse models with mitochondrial DNA (mtDNA) defects- MitoPark and ND6P25L. MitoPark mice have a DA-specific deletion of TFAM (transcription factor A mitochondrial, which causes mitochondrial dysfunction, the release of mtDNA, and constitutive activation of STING signaling, resulting in neuroinflammation and progressive nigrostriatal deterioration within 6mo. of age. The complex I ND6P25L mutation causes progressive slowing of EEG, loss of REM sleep, L-DOPA-responsive bradykinesia, and increased sensitivity to immune challenge. Our PET/CT results show that [18F]ROStrace increases early in the course of PD-like pathology in both models, preceding DA-degeneration and correlating with microglial activation. In addition, ROStrace retention is increased 78% in young ND6P25L mice after peripheral LPS injection, which accelerated the motor impairment and neuroinflammation. Together, our results demonstrate the potential of [18F]ROStrace as a first-in-class PET tracer for quantifying mito-immune stress in the prodromal phase of neurodegenerative disease. [18F]ROStrace may enhance clinical trial design by identifying at-risk PD patients who are most likely to benefit from mitochondrial therapeutics.

**Disclosures: Y. Zhu:** None. **A. Young:** None. **N. Kohli:** None. **C. Hsieh:** None. **M. Sheldon:** None. **J. Coni:** None. **S. Li:** None. **H. Lee:** None. **D. Wallace:** None. **R. Mach:** None. **M.J. McManus:** None.

**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.27/D63

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Neurotoxic human iPSC-astrocytes and gene expression network analysis to identify drug targets for neurodegenerative diseases

**Authors:** H. KOBAYASHI[1], K. MAEDA[2], K. KAZETANI[2], A. NABETANI[1], ***S. ENDOH-YAMAGAMI**[1];
[1]Bio Sci. & Engin. Labs., [2]Imaging Technol. Ctr., FUJIFILM Corp., Kanagawa, Japan

**Abstract:** Astrocytes are getting attention for their involvement in neuroinflammation and etiology of neurodegenerative diseases. To enable drug development targeting astrocytes, we establish a method to induce neurotoxic astrocytes and gene network analysis. We performed gene network analysis using a public gene expression dataset of the brains from healthy people of various ages, and we confirmed that reactive astrocyte gene expression is induced around age of 60 following to microglial gene induction starting from ages of 30 to 40. To reproduce the neurotoxic reactive astrocytes, we first treated human iPSC-astrocytes (hiPSC-astrocytes) with IL-1a, TNFa, and C1q, which are reported to induce the neurotoxic reactive state in mouse astrocytes (Liddelow et al., 2017). The three factors induced the expression of the complement component 3 (C3) gene, a typical marker of reactive astrocytes, to some extent, but they did not lead hypertrophic morphology or neurotoxicity in hiPSC-astrocytes. We speculated that the difference was due to species difference in cytokine response between rodents and human. We looked for different combinations of cytokines, and we found a condition to induce strong neurotoxicity in human astrocytes. Using the condition, we screened for compounds that inhibit acquisition of neurotoxicity, and we identified compounds including JAK inhibitors. For target validation, we performed gene knockdown, and we found that JAK1 knockdown was enough to inhibit neurotoxicity induction. To understand neurotoxicity induction mechanism in more detail, we ran gene network analysis using a gene expression dataset of hiPSC-astrocytes treated with neurotoxicity inducing factors. By knockdown about 500 genes selected from the network, we identified a novel target gene involved in astrocyte neurotoxicity. The target reliability was further confirmed using target inhibitors. These results indicate that the combination of neurotoxic hiPSC-astrocyte induction and gene network analysis is a powerful tool to develop new drugs for neurodegenerative diseases and other nervous system related disorders.

**Disclosures:** **H. Kobayashi:** A. Employment/Salary (full or part-time); FUJIFILM corporation. **K. Maeda:** A. Employment/Salary (full or part-time); FUJIFILM corporation. **K. Kazetani:** A. Employment/Salary (full or part-time); FUJIFILM corporation. **A. Nabetani:** A. Employment/Salary (full or part-time); FUJIFILM corporation. **S. Endoh-Yamagami:** A. Employment/Salary (full or part-time); FUJIFILM corporation.

**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.28/D64

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH231

**Title:** Inflammatory cytokines induce dysfunctional astroglial exosome signaling to motor neurons in SOD1G93A

**Authors: *S. JIN**[1], J. HACKER[2], Y. TIAN[3], J. HU[2], Y. YANG[1];
[1]Tufts university, Boston, MA; [2]Neurosci. Dept., Tufts Univ., Boston, MA; [3]Tufts Univ. Sch. of Med., Boston, MA

**Abstract:** Exosomes are small vesicles of the endosome origin released by various cell types, including neurons and glial cells in the central nervous system (CNS). They have been implicated in the clearance and spreading of toxic proteins associated with neurodegenerative diseases. However, the role of astroglia-specific exosomes in the progression of amyotrophic lateral sclerosis (ALS) remains less understood. In current study, by selectively isolating exosomes using size-exclusion chromatography (SEC) and the next generation ZetaView nanoparticle tracking analysis (NTA), we showed that treatment of inflammatory cytokine mixture ITC (IL1a, TNFa, and C1q) significantly reduces exosome secretion from both NTg and SOD1G93A$^{+}$ astrocyte cultures. Although mutant hSOD1 protein has been detected in astroglial exosomes (A-Exo) isolated by ultracentrifugation, we found no mutant hSOD1 or misfolded SOD1 proteins in SEC-isolated SOD1G93A$^{+}$ A-Exo. SEC-isolated A-Exo are protective against glutamate-induced excitotoxicity in cortical neurons and SOD1G93A$^{+}$ spinal motor neurons, which is completely diminished by the pre-treatment of ITC mixture. In addition, ITC-NTg A-Exo. also selectively induces death of SOD1G93A$^{+}$ (but not cortical neurons or SOD1G93A$^{-}$) spinal motor neurons. Subsequent proteomic analysis of NTg, ITC-NTg, SOD1G93A, and ITC-SOD1G93A A-Exo. found that protein cargoes in A-Exo. is drastically altered by both ITC pre-treatment and overexpression of hSOD1G93A. In particular, glia-specific cell adhesion protein HepaCAM is significantly down-regulated in A-Exo by the ITC pre-treatment. Genetic and biochemical studies with HepaCAM-deficient A-Exo prepared from HepaCAM KO mice further showed that HepaCAM is essential in mediating protective effect of NTg A-Exo against glutamate-induced excitotoxicity. By employing cell-type specific exosome reporter mice (hCD63-copGFP$^{f/f}$) and a single and focal injection of AAV2/5-GFAP-Cre into the ventral horn of spinal cords, we further examined the in vivo changes of A-Exo in the SOD1G93A ALS model. We observed long-distance spreading of astrocyte-derived exosomes from the focal injected area in the spinal cord of NTg and SOD1G93A mice. Interestingly, the overall spreading distance of A-Exo is reduced in diseased (P100-110) SOD1G93A mice compared to age-matched NTg mice. Taken together, our current study reveals that inflammatory cytokines (and hSOD1G93A mutant) induces dysfunction of A-Exo through the reduced surface HepaCAM expression, providing a new mechanism about the role of A-Exo in ALS and how cytokines contribute to motor neuron and axon neurodegeneration in ALS.

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**Poster**

**PSTR011. Neuroimmune Mechanism of Neurodegeneration**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR011.29/D65

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Noninvasive gamma stimulation modulates AQP4 polarization and recruits vasoactive peptide signaling in 5XFAD mice

**Authors: *F. GALIANA-MELÉNDEZ**[1,2], M. MURDOCK[1,2], C.-Y. YANG[1,2], N. SUN[3,4], P.-C. PAO[1,2], C. BLANCO-DUQUE[1,2], M. KAHN[1,2], N. LAVOIE[1,2], M. VICTOR[1,2], M. ISLAM[1,2], N. LEARY[1,2], S. WANG[1,2], A. BUBNYS[1,2], E. MA[1,2], L. AKAY[1,2], T. KIM[1,2], M. SNEVE[5], Y. QIAN[5], C. LAI[6], M. MCCARTHY[7], N. KOPELL[7], M. KELLIS[4,3], K. PIATKEVICH[5,6], E. BOYDEN[5], L.-H. TSAI[1,2,3];
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**Abstract:** The glymphatic system clears metabolic waste from the brain, which is impaired in aging and Alzheimer's disease (AD). In this study, we investigated the effects of multisensory gamma stimulation on glymphatic clearance of amyloid clearance in the 5XFAD mouse model of AD. snRNA-seq following 1 hour of noninvasive gamma stimulation in 6-month-old 5XFAD mice revealed transcriptional changes in several cell types, including upregulation of genes related to ion buffering in astrocytes. High resolution imaging revealed gamma stimulation promotes the polarization of AQP4, which is known to be important for glymphatic clearance. We also identified upregulation of genes related to neuropeptides in vasoactive intestinal peptide (VIP) neurons. Chemogenetically attenuating VIP neuronal signaling abolished the amyloid clearance effects of gamma stimulation in 6-month-old 5XFAD mice. These findings provide novel insights into AQP4- and VIP-dependent mechanisms underlying glymphatic clearance of amyloid by noninvasive gamma stimulation.

**Disclosures:** **F. Galiana-Meléndez:** A. Employment/Salary (full or part-time); The Picower Institute for Learning and Memory. **M. Murdock:** None. **C. Yang:** None. **N. Sun:** None. **P. Pao:** None. **C. Blanco-Duque:** None. **M. Kahn:** None. **N. Lavoie:** None. **M. Victor:** None. **M. Islam:** None. **N. Leary:** None. **S. Wang:** None. **A. Bubnys:** None. **E. Ma:** None. **L. Akay:** None. **T. Kim:** None. **M. Sneve:** None. **Y. Qian:** None. **C. Lai:** None. **M. McCarthy:** None. **N. Kopell:** None. **M. Kellis:** None. **K. Piatkevich:** None. **E. Boyden:** None. **L. Tsai:** None.

**Poster**

**PSTR012. APP/Abeta Pathway: Cellular and Animal Models I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR012.01/D66

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

**Support:** NIH R01AA025718
Fondecyt-1221080
PhD ANID fellowship-21202521

**Title:** Early reduction of long-term depression in the nucleus accumbens of a transgenic Alzheimer's disease mouse model

**Authors: *N. RIFFO-LEPE**, M. KONAR-NIÉ, J. GONZALEZ-SANMIGUEL, S. GALLEGOS, E. J. FERNANDEZ-PÉREZ, L. G. AGUAYO;
Univ. of Concepcion, Concepcion, Chile

**Abstract:** Alzheimer's disease (AD) is a progressive neurological disorder that leads to dementia in an increasingly aging population. Recent evidence indicates synaptic dysfunction and impairment of the limbic circuit in the early stages of the disease, even before the deposition of amyloid plaques, where intracellular Aβ (iAβ) has been reported. The nucleus accumbens (nAc) is a key component of the limbic reward system, involved in cognitive and emotional behavior such as pleasure, apathy, and motivation, all of which are affected in AD. However, the effects of the early iAβ accumulation in the nAc on synaptic transmission, plasticity, and excitability of medium spiny neurons (MSNs) remain unclear. We first performed immunofluorescence analysis on brain slices from 3-month-old WT and APP/PS1 (2xTg) mice and found abundant iAβ, but no extracellular plaques in the nAc. To investigate whether the early presence of iAβ influences synaptic transmission and neural plasticity in the nAc, we carried out patch-clamp electrophysiology on brain slices. Here, we applied a high frequency stimulation (HFS) protocol to induce long-term depression (LTD) in the nAc of 3- and 6-month-old WT and 2xTg mice. No significant differences were observed in the percentage of LTD between the two genotypes at 3 months. Interestingly, LTD was strongly decreased in 6-month 2xTg mice (WT: 47 ± 8% vs. 2xTg: 11 ± 6%). Additional analysis of synaptic transmission in MSNs showed no significant changes in the frequency of the mEPSCs at 3 and 6 months between WT and 2xTg mice, thereby discarding presynaptic mechanisms involved in the decrease in LTD. Furthermore, to examine synaptic strength, we measured the ratio of AMPAR- and NMDAR-EPSC amplitude in 6-month-old WT and 2xTg brain slices and found a significant decrease in the AMPA/NMDA ratio in the 2xTg mice (WT 1.5 ± 0.3 vs. 2xTg 0.9 ± 0.1), suggesting a postsynaptic mechanism for the reduced LTD. To further explore if the early postsynaptic effects of amyloid pathology in the nAc were selective, we analyzed passive and active membrane properties recording evoked action potentials (APs) elicited by current injection in brain slices. The data showed a significant increase in the frequency of APs in the 2xTg mice accompanied by a decrease in amplitude, with no change in threshold, duration, or resting membrane potential. Overall, these findings indicate that accumbal MSNs are an early brain target of amyloid pathology, with impaired synaptic plasticity and neural excitability, and suggest that AD pathology might initiate in mesolimbic areas contributing to non-psychiatric symptoms, such as apathy and loss of motivation.

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**Poster**

**PSTR012. APP/Abeta Pathway: Cellular and Animal Models I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR012.02/D67

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

**Support:** AG064465

**Title:** Sleep Abnormalities in Down Syndrome and Alzheimer's Disease

**Authors: *R. A. MILSTEAD**[1], H. WONG[3], J. LEVENGA[5], J. M. BUCK[4], C. BORSKI[1], K. KASTENGREN[1], L. LAPLANTE[1], A. COOPER-SANSONE[1], J. HANSON[6], P. CAIN[2], M. R. OPP[4], C. HOEFFER, Jr.[4];
[1]Integrative Physiol., [2]Univ. of Colorado, Boulder, Univ. of Colorado, Boulder, Boulder, CO; [3]PTC Therapeutics, Inc., Univ. of Colorado Boulder, Bridgewater, NJ; [4]Univ. of Colorado Boulder, Univ. of Colorado Boulder, Boulder, CO; [5]Horizon Discovery, Horizon Discovery, Lafayette, CO; [6]Integrative Physiol., CU Boulder, Boulder, CO

**Abstract: Abstract**There is a bidirectional relationship between Alzheimer's disease (AD) and sleep: sleep disturbances increase AD risk, and AD is associated with sleep disturbances. Down Syndrome (DS) is associated with sleep abnormalities and highly penetrant, early-onset AD (DS-AD). Factors involved in early onset DS-AD may also play a role in the manifestation of sleep and circadian disturbances in DS, which could promote the development of AD neuropathology. We aim to determine the role of trisomy 21 gene overexpression in sleep, cognitive, synaptic, and AD-related pathology in a mouse model of DS (Dp16). In theory, the sleep abnormalities, and cognitive deficits in the Dp16 mice could be caused solely by triplication of the App gene. Even so, this hypothesis has never been formally tested. However, our published and unpublished data suggest that another chromosome 21 gene triplicated in DS, Regulator of calcineurin1 (Rcan1), may contribute to or drive these phenotypes. RCAN1 is a crucial regulator of the phosphatase calcineurin (CaN), and DS-associated neurological deficits may be partly linked to abnormal neural CaN activity. CaN controls many neurobiological processes such as cognition, sleep, and circadian function. We have previously shown that mice overexpressing a human RCAN1 isoform show early age tau pathology and cognitive and synaptic defects. We now have new evidence demonstrating age-dependent sleep and circadian abnormalities in RCAN1TG mice and rescue of sleep deficits in Dp16 mice following the restoration of RCAN1 expression. Our central hypothesis is that RCAN1 triplication in DS promotes sleep disturbances and exacerbates AD-related pathology, and we will test this hypothesis using *Rcan1* and *App* gene dose-corrected Dp16 animals.

**Disclosures: R.A. Milstead:** None. **H. Wong:** None. **J. Levenga:** None. **J.M. Buck:** None. **C. Borski:** None. **K. Kastengren:** None. **L. LaPlante:** None. **A. Cooper-Sansone:** None. **J. Hanson:** None. **P. Cain:** None. **M.R. Opp:** None. **C. Hoeffer:** None.

**Poster**

**PSTR012. APP/Abeta Pathway: Cellular and Animal Models I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR012.03/D68

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

**Support:** 1R21AG079292-01

**Title:** Spatial working memory in pig models of Alzheimer's disease lacking functional PSEN1

**Authors: *D. A. MURPHY**[1], L. M. ALLEN[1], M. CAPOTE[1], J. VARGAS[1], T. J. JAROME[2], K. LEE[3], T. A. ALLEN[1];
[1]Florida Intl. Univ., Miami, FL; [2]Virginia Tech., Virginia Tech., Blacksburg, VA; [3]Univ. of Missouri, Columbia, MO

**Abstract:** Alzheimer's Disease (AD) is the leading cause of dementia in the United States. While progress has been made using rodent AD models, there is a need to validate large animal models of AD to better understand the disease process in animals that are more like humans. Pigs have long been regarded as the ideal preclinical model for drug development in biomedical research due to their substantial similarities to humans across major organ systems, and are increasingly favored in translational neuroscience (e.g., traumatic brain injury, neurotoxicity). However, pig AD models have yet to be generated that reflect human behavioral symptoms. Thus, we developed a pig model of AD by manipulating the Presenilin-1 gene (*PSEN1*) because human mutations of this gene are the most common cause of early-onset familial AD (FAD). *PSEN1* encodes the catalytic subunit of the gamma-secretase enzyme, which breaks down amyloid beta precursor protein (APP) into smaller subunits, including beta-amyloid (Aβ) peptides. Mutations of *PSEN1* increase the production of Aβ42, the more toxic form that is prone to aggregation and formation of the dense, insoluble oligomers known as “plaques” that are a hallmark pathology of AD. We created a pig model lacking functional *PSEN1* by using CRISPR/Cas9 system and began validating them for cognitive and molecular characteristics of AD. In the cognitive domain, our expectation was that *PSEN1* pigs would have memory deficits compared to controls, especially in spatial and working memory domains. Here, we tested pigs in using a fully automated T-maze apparatus (17’ x 13’) designed to tax spatial working memory in which pigs were rewarded for correctly alternating choices at the T-junction. Our evaluations focused on the delayed spatial alternation task, which forced pigs to wait in the starting area during randomized delays (from 5 sec to 240 sec) and burdened spatial working memory. We did not observe differences in *PSEN1* and control pigs at the shortest delays, suggesting they were similarly capable and motivated to alternate for the food reward. However, *PSEN1* pigs were significantly impaired at longer delays (≥60 sec), demonstrating a spatial working memory deficit. This pattern of results is reminiscent of memory deficits in rodent AD models and in mild-to-moderate stages of AD human patients. We are also investigating the molecular and histological characteristics (brain and blood) in the *PSEN1* pigs to compare with markers in AD patients. This work is a part of a larger program to establish pigs as a model species for behavioral neuroscience and specifically towards translational goals to better understand AD progression, pathology, and therapeutic interventions.

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**Poster**

**PSTR012. APP/Abeta Pathway: Cellular and Animal Models I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR012.04/D69

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

**Support:** Swedish Research Council
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Stohne's Foundation
King Gustaf V's and Queen Victoria's Freemason Foundation
Golje's Foundation
The Tanz Family
Knut and Alice Wallenberg Foundation

**Title:** Characterization of the Uppsala APP deletion transgenic mouse model

**Authors: *M. INGELSSON**[1], M. PAGNON DE LA VEGA[2], S. SYVÄNEN[2], M. HOOLEY[3], V. GIEDRAITIS[2], E. KONSTANTINIDIS[2], J. ERIKSSON[2], X. AGUILAR[2], T. SPIRES-JONES[3], L. LANNFELT[2], L. N. NILSSON[4], A. ERLANDSSON[2], G. HULTQVIST[2], D. SEHLIN[2];
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**Abstract:** Plaques of amyloid-beta (Aβ) is one of the main pathological features in the Alzheimer's disease (AD) brain. Early-onset familial forms of AD (FAD) caused by mutations in the gene for the amyloid precursor protein (*APP*) result in pathology by altering Aβ production or by generating aggregation-prone Aβ species. Recently, we identified the *Uppsala APP* deletion (*APPUpp*), which is pathogenic by a triple mechanism. In addition to an increased β-secretase and an altered α-secretase APP cleavage, leading to increased overall levels of Aβ, the mutant species adopt a unique conformer that undergoes a rapid aggregation and deposition process. Here, we aimed to further explore the effects of *APPUpp in vivo* to increase our knowledge of the pathophysiological mechanisms of this FAD mutation. We generated a transgenic mouse model (tg-UppSwe), which expresses human *APP* with the *APPUpp* deletion, together with the *APPSwe* mutation (to increase total Aβ expression). The amount of Aβ pathology was analyzed in mouse brains at different ages. Moreover, *in vivo* amyloid-PET imaging was conducted in aged tg-UppSwe mice. Finally, glial responses to Aβ pathology was

studied in the mouse brain tissues. At 5-6 months, tg-UppSwe mice displayed an increased β-secretase cleavage and a suppressed α-secretase cleavage, associated with the formation of diffuse plaques that were dominated by the mutated version of Aβ42 (AβUpp1-42$_{\Delta 19\text{-}24}$). Contrary to what has been seen for several other tg APP models, tg-UppSwe mice were [$^{11}$C]PiB-PET negative. Moreover, tg-UppSwe mice did not display any clear glial responses to Aβ pathology. In summary, the tg-UppSwe mouse model recapitulates previously reported pathological features of brains from *Uppsala APP* mutation carriers. Interestingly, the presumed structural properties of AβUpp1-42$_{\Delta 19\text{-}24}$ aggregates make them negative for [$^{11}$C]PiB-PET and less apt to elicit Aβ-mediated glial responses.

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**Poster**

**PSTR012. APP/Abeta Pathway: Cellular and Animal Models I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR012.05/D70

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

**Support:** Freemasons New Zealand 3726531
BRNZ scholarship
University of Auckland doctoral scholarship

**Title:** Sheep models of Alzheimer's Disease

**Authors: *N. E. MCKEAN**[1], C. MCMURRAY[1], R. R. HANDLEY[1], C. MCLAUGHLAN[2], S. R. RUDIGER[2], J. KELLY[2], H. ZETTERBERG[3], J. PEARSON[4], S. REID[1], P. VERMA[2], J. F. GUSELLA[5], M. J. OWEN[6], J. A. HARDY[7], H. J. WALDVOGEL[8], R. L. FAULL[9], S. BAWDEN[2], R. G. SNELL[1];
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**Abstract:** Alzheimer’s disease (AD) is a devastating neurodegenerative disease. The prevalence is rapidly increasing due to an ageing population worldwide, creating a looming population health crisis. Many rodent models of AD have been created, but none capture the full symptomatology without massively overexpressing multiple human mutations in transgenes. The aim of this project was to create large animal models of AD with single mutations in native

genes. Sheep have larger bodies and a gyrencephalic brain similar to human. Importantly, they naturally develop plaques and tangles as they age. Major AD-related genes, such as *APP*, *PSEN1* and *PSEN2*, and the *APP* cleavage sites which produce the Aβ peptide, are highly conserved between human and sheep. Also and importantly, sheep are naturally fixed for the APOE4 allele associated with late onset AD in humans. They can also be efficiently bred in large numbers and simply maintained in a normal farming situation. Two gene edited sheep lines were produced by injection of CRISPR-Cas9 RNP complexes, including a single strand donor DNA carrying the *PSEN1* E280A or *APP* Swedish mutation, into single cell zygotes, which were then implanted. Five founder animals were born carrying the *PSEN1* E280A mutation. One ewe is homozygous, two ewes are heterozygous, and two rams are hemizygous with frameshift mutations on their non-E280A allele. Two rams were heterozygous for the *APP* Swedish mutation. The founder lambs were genotyped by PCR and whole genome sequenced to confirm zygosity. No off-target editing was detected. All animals are outwardly healthy and growing normally. Repeated plasma biomarker analysis of the *PSEN1* E280A animals revealed that $A\beta_{1-42}$:$A\beta_{1-40}$ peptide ratios are increased in the mutation carriers. The *APP* Swedish lambs had greatly enhanced $A\beta_{1-40}$ and $A\beta_{1-42}$ concentrations. Both of these phenotypes correspond with human mutation carriers. For the *PSEN1* E280A founders, one heterozygous ewe and one ram have been used to create $F_1$ lines carrying the mutation. The mutation carrying offspring from the ewe lamb have inherited the Aβ biomarker phenotype, as expected. The offspring from the ram have just been born and will be part of a life history study. For the *APP* Swedish founders, one ram has been used to create an $F_1$ line, which will also be part of a natural history study. If these animals can recapitulate the entire disease from a single gene cause, they will likely shed light on the underlying mechanisms of AD that have proven elusive with small animal models. These animals are also likely to be useful for preclinical pharmaceutical testing.

**Disclosures:** **N.E. McKean:** None. **C. McMurray:** None. **R.R. Handley:** None. **C. McLaughlan:** None. **S.R. Rudiger:** None. **J. Kelly:** None. **H. Zetterberg:** None. **J. Pearson:** None. **S. Reid:** None. **P. Verma:** None. **J.F. Gusella:** None. **M.J. Owen:** None. **J.A. Hardy:** None. **H.J. Waldvogel:** None. **R.L. Faull:** None. **S. Bawden:** None. **R.G. Snell:** None.

**Poster**

**PSTR012. APP/Abeta Pathway: Cellular and Animal Models I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR012.06/E1

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

**Support:** AMED JP19dm0207092h0001

**Title:** Generation of a transgenic common marmoset model of Alzheimer’s disease

**Authors: *E. N. MINAKAWA**[1], N. KOHRI[3], T. NAKATANI[1], J. OGURA[1], M. SHIDAHARA[4], K. IKEGAMI[3], A. KAWANOBE[1], Y. NAKAMURA[1], A. KOSUGI[1], H. YAGIHARA[1], S. GAOWA[3], T. TAKEUCHI[5], Y. SAITO[6], K. KATO[2], I. TOMIOKA[3], K.

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**Abstract:** Alzheimer's disease (AD) is the leading cause of dementia worldwide. Translational research of AD has faced challenges due to genetic, anatomical, and physiological differences between humans and rodents used in preclinical studies. Establishment of more relevant AD models is awaited. Recent gene modification techniques enabled the generation of genetically modified NHPs including common marmosets. We previously established a transgenic marmoset model of polyglutamine (polyQ) disease, a neurodegenerative disease, recapitulating behavioral and neuropathological abnormalities. In this study, we aimed to generate a transgenic marmoset model of AD harboring human *APP* and *PS1* genes with causative mutations for familial AD (FAD) under a systemic (CMV) or neuron-specific (CamKII) promoter. CamKII promoter was used to eliminate the systemic toxicity of the overexpressed protein observed in our polyQ disease model. A lentiviral vector carrying either of these promoters and the transgene was injected into marmoset embryos, which were transferred to surrogate mothers. Out of 19 surrogates, ten became pregnant, and nine delivered a total of 12 offspring. Embryonic developmental rate was higher than the polyQ disease model, possibly due to lower cytotoxicity of the transgenic product compared with polyQ proteins. Eight out of the 12 offspring carried and expressed the transgene in skin fibroblasts derived from each offspring. Notably, one second-generation offspring carried the transgene. Using these marmosets, longitudinal phenotypic assessment is ongoing. Plasma and cerebrospinal fluid were longitudinally collected from 3 and 12 months of age, respectively, and were subjected to AD biomarker measurement, such as amyloid β (Aβ), phosphorylated tau, and neurofilament light chain, using ultrasensitive enzyme-linked immunosorbent assay. Brain positron emission tomography (PET) scan using tracers for Aβ and neuroinflammation was performed at 12 months of age. Additional PET scan including tracers for tau is scheduled at 24 months of age. Continuous monitoring of the circadian rhythm and sleep-wake patterns was performed using an infrared sensor. This novel marmoset model of AD may bridge the translational gap and facilitate the development of effective disease-modifying treatments for AD.

**Disclosures: E.N. Minakawa:** None. **N. Kohri:** None. **T. Nakatani:** None. **J. Ogura:** None. **M. Shidahara:** None. **K. Ikegami:** None. **A. Kawanobe:** None. **Y. Nakamura:** None. **A. Kosugi:** None. **H. Yagihara:** None. **S. Gaowa:** None. **T. Takeuchi:** None. **Y. Saito:** None. **K. Kato:** None. **I. Tomioka:** None. **K. Seki:** None.

**Poster**

**PSTR012. APP/Abeta Pathway: Cellular and Animal Models I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR012.07/E2

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

**Support:** HU21C0157

**Title:** Ebp1 depletion in mice forebrain elicits the phenotypes of Alzheimer's disease : proposing a novel animal model of Alzheimer's disease

**Authors: *B.-S. KIM**[1], J.-Y. AHN[2];
[1]Sungkyunkwan Univ. Sch. of Med., Suwon, Korea, Republic of; [2]Mol. Cell Biol, Sungkyunkwan Univ. Sch. Med., Suwon, Kyonggi-do, Korea, Republic of

**Abstract:** Alzheimer’s disease (AD) is a neurodegenerative disease characterized by abnormal protein deposits, progressive memory loss, cognitive impairment and body malfunction, which eventually leads to death. Despite the increasing prevalence and long study periods of AD, no AD mouse model fits sporadic late-onset AD (LOAD) phenotypes without any genetic mutations. Here, we introduce forebrain-specific *Ebp1* knockout mice as a novel AD murine model. *Ebp1* deletion in cortex and hippocampus via Camk2a-cre driver induces prominent neuronal cell death, declined learning and memory function, elevated amyloid beta (Aβ) accumulations and neurofibrillary tangles (NFT). Furthermore, GFAP-positive astrocytes were increased in hippocampus of 10M *Ebp1*-CKO, indicating neuroinflammatory responses. Ebp1 is greatly reduced and inversely correlated with Aβ in the brains of 5x FAD mice, the representative animal model of AD, and human AD patients. Interestingly, Ebp1 has protective effects on APP cleavage and loss of *Ebp1* elicits the failure to block the interaction between APP and Presenilin (PS), a catalytic core of γ-secretase, in AD conditions. Reinstatement of *Ebp1*-WT into Ebp1-null mice brain or 5x FAD brains result in alleviation of Aβ production, along with cognitive improvement. In this study, we explore the progressive neuropathological phenotypes in aged $Ebp1^{Camk2a\text{-}cre}$ mice, proposing a potential for LOAD mouse model. Moreover, we suggest that functional Ebp1 maintenance is a novel therapeutic target by interrupting the association APP with PS.

**Disclosures: B. Kim:** None. **J. Ahn:** None.

**Poster**

**PSTR012. APP/Abeta Pathway: Cellular and Animal Models I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR012.08/E3

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

**Support:** NIH Grant NS115898

**Title:** Novel Signaling Mechanisms Regulated by Amyloid Precursor Proteins May Help Control Neuronal Migration And Guidance In The Developing Nervous System

**Authors: *P. F. COPENHAVER**;
Cell and Developmental Biol., Oregon Hlth. & Sci. Univ. Neurosci. Grad. Program, Portland, OR

**Abstract:** Although Amyloid Precursor Protein (APP) is best known as the source of beta amyloid peptides that accumulate in Alzheimer's Disease (AD), APP can also regulate a variety of important functions in the developing and mature nervous system, including neuronal migration, synaptogenesis and plasticity, and adaptive responses following injury. Early studies in cell culture suggested that APP can act as an unconventional G protein-coupled receptor that stimulates the heterotrimeric G protein G-alpha-o (Go) to induce calcium-dependent responses, while chronic activation provoked calcium overload and apoptosis. Some APP mutations linked with familial forms of AD can also provoke Go hyperactivation in cell culture, while elevated G protein activity in the brain correlates with the severity of cognitive decline in AD patients. However, authentic roles for APP-Go signaling have remained controversial. We have used Manduca as model system to demonstrate that insect APP (APPL) regulates neuronal migration in the developing enteric nervous system (ENS) via Go-dependent pathways. APPL and Go colocalize in the leading processes of migratory neurons, similar to APP-Go colocalization in cultured mouse hippocampal neurons. APP family proteins also co-immunoprecipitate with Go from insect and mammalian brain lysates (including human samples), while expressing split-GFP-tagged constructs of APPL and Go in Drosophila showed that they directly interact in vivo. In addition, Manduca Contactin is expressed by ensheathing glial cells and functions as a ligand for neuronal APPL, aligning with evidence that mammalian Contactins also bind APP family proteins. These results demonstrate that Manduca provides a useful discovery system for interrogating the mechanisms of this evolutionarily conserved pathway. We have now identified two candidate effectors for APP-Go signaling. One candidate is RhoGEF2, an ortholog of mammalian PDZ-RhoGEFs that activates the small GTPase RhoA. Initial studies suggest that APPL engagement induces Go-dependent stimulation of RhoGEF2, resulting in RhoA activation. The second candidate is TRPL, an insect ortholog of TRP family channels that induces calcium-dependent retraction responses. Notably, TRP channels also interact with APP family proteins in mouse brain. We are currently investigating how the coordinated engagement of these two effector pathways provides integrated responses to APP signaling in the developing nervous system. In turn, by deciphering the normal mechanisms of APP-Go signaling in this model system, this work may also help identify new targets for treating diseases like AD in which this pathway is misregulated.

**Disclosures: P.F. Copenhaver:** None.

**Poster**

**PSTR012. APP/Abeta Pathway: Cellular and Animal Models I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR012.09/E4

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

**Support:** NIH Grant NS085171
NIH Grant NS086965

**Title:** Regulators of paraventricular oxytocin expression in amyloid precursor protein transgenic mice

**Authors: *C. ST. ROMAIN**[1], C.-H. FU[1], T. PUNNEN[2], J. CHIN[1];
[1]Baylor Col. of Med., Houston, TX; [2]Rice Univ., Houston, TX

**Abstract:** Alzheimer's Disease (AD) is a heterogeneous disease diagnosed clinically by memory impairment and cognitive decline. The presence of amyloid plaques and neurofibrillary tangles on autopsy provides a definitive diagnosis. However, a subset of cognitively intact individuals also has significant AD neuropathology on autopsy. To identify factors driving such cognitive resilience to AD neuropathology, we studied transgenic mice expressing mutant human amyloid precursor protein (APP mice, Line J20). Despite a similar history of spontaneous seizure activity as their susceptible APP littermates, approximately 30% of these mice develop resilience. Resilient APP mice stop having seizures and epileptiform activity and exhibit normal spatial memory around 3 months of age, while their susceptible littermates exhibit progressively worsening memory and continued seizure activity. Resilient and susceptible APP littermates also produce amyloid β (Aβ) and develop plaques with the same time course. To investigate genetic factors driving this phenotypic divergence, we examined an RNA-seq dataset generated using dentate gyrus samples from resilient APP mice, susceptible APP mice, and nontransgenic (NTG) littermate controls. We identified oxytocin receptor (Oxtr) as a potential resiliency factor, as it was decreased in the resilient group compared to both susceptible and NTG groups. Because reductions in Oxtr expression can be driven by increased oxytocin signaling, we hypothesized that resilient APP mice with decreased Oxtr might have higher oxytocin levels. Using immunohistochemistry, we identified a concomitant increase in oxytocin-expressing cells of the paraventricular nucleus (PVN) of the hypothalamus in resilient APP mice. To determine what upstream genetic changes might be driving increased oxytocin expression, we investigated activity-dependent genes. We focused on the activity-induced transcription factors c-fos and ΔFosB given the seizure history present in APP mice and the critical roles played by ΔFosB in regulating gene expression in APP mice. We identified co-labeling of ΔFosB and oxytocin in the PVN of APP mice, suggesting ΔFosB could play a role in regulating oxytocin expression. Given oxytocin's role in social behavior and evidence that social interaction can delay AD onset and help to mitigate cognitive decline, identifying and manipulating genetic regulators of oxytocin expression could prove therapeutically beneficial in conferring resilience to AD progression.

**Disclosures: C. St. Romain:** None. **C. Fu:** None. **T. Punnen:** None. **J. Chin:** None.

**Poster**

**PSTR012. APP/Abeta Pathway: Cellular and Animal Models I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR012.10/E5

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

**Support:** NIH 1RF1AG062166

**Title:** Effects of chronic stress on amyloid and tau pathologies in animal models of Alzheimer's disease

**Authors: *M. MISHU**, Y. LEI, X. LU;
Med. Col. of Georgia at Augusta Univ., Augusta, GA

**Abstract:** Alzheimer's disease (AD) is a progressive neurodegenerative disorder, which is pathologically characterized by extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles composed of highly phosphorylated tau. The exact cause of AD remains unknown; however, it is believed to arise from an intricate interplay between genetic and environmental factors. While prolonged exposure to high levels of stress increases the risk for the development or progression of the disease, the specific underlying mechanisms remain yet to be identified. Thus, the objective of this study was to investigate the effects of chronic stress on Aβ and tau pathology in different brain regions of mouse models overexpressing mutant human APP, PS1 and tau proteins at different ages. Experiments are currently underway to evaluate the effects of different types of stress on the progression of neuro pathologies and associated cognitive impairment. Future studies will identify the sites and mechanisms of stress hormones in both APP and tau mouse models

**Disclosures: M. Mishu:** None. **Y. Lei:** None. **X. Lu:** None.

**Poster**

**PSTR012. APP/Abeta Pathway: Cellular and Animal Models I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR012.11/E6

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

**Support:** CIHR grant: #PJT-169197

**Title:** Behavioral deficits and mitochondrial damage in locus coeruleus (LC) neurons in a pseudo phosphorylated human tau rodent model of Alzheimer's disease

**Authors: J. PICHE**[1], A. FLYNN[2], C. HEMSWORTH[2], T. OMOLUABI[1], Q. YUAN[1], *A. C. W. WEEKS[3];
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**Abstract:** Early neural evidence of Alzheimer's disease (AD) involves abnormally phosphorylated pre-tangle tau proteins in locus coeruleus (LC) neurons. Cellular toxicity and mitochondrial damage via aggregation of these abnormal tau proteins are thought to induce neurodegeneration early in the progression of AD by compromising metabolic resources in LC

neurons, potentially through its effect on L-type calcium channels. In the current study, behavioral and cognitive functions, along with mitochondrial ultrastructure, were analyzed in a human pre-tangle tau rat model. We infused an adeno-associated viral vector carrying a human tau gene pseudo phosphorylated at 14 sites in 5-month-old TH-Cre rats. Behavioral testing, which took place 10 months post-infusion, showed poorer performance in the spatial and odor discrimination tasks in the pseudo phosphorylated human tau infused animals. Following behavioral testing, the animals were perfused, and tissue was embedded for transmission electron microscopy (TEM). Mitochondrial ultrastructural damage was assessed in LC neuronal cell bodies. Results demonstrated a significant increase in mitochondrial damage in the tau infused rodents. These results have the potential to significantly advance our understanding of the early involvement of mitochondrial damage in AD which may lead to earlier detection and potentially, novel therapies for this devastating disease.

**Disclosures: J. Piche:** None. **A. Flynn:** None. **C. Hemsworth:** None. **T. Omoluabi:** None. **Q. Yuan:** None. **A.C.W. Weeks:** None.

**Poster**

**PSTR012. APP/Abeta Pathway: Cellular and Animal Models I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR012.12/E7

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

**Support:** NSERC Graduate Scholarship - Doctoral
CAMH Discovery Fund

**Title:** Assessing the impact of sleep disruption on cognition, stress, and proteostasis in transgenic AD mouse models

**Authors: *D. WEAR**[1,2], C. D. MORRONE[2], D. SIMPSON[1,2], F. AZHAR[5,3], A. SEREGIN[5,3], R. ALAM[6,2], H. YU[1,2,4];
[1]Pharmacol. & Toxicology, Univ. of Toronto, Toronto, ON, Canada; [2]Brain Hlth. Imaging, [4]Geriatric Mental Hlth. Res. Services, [3]Ctr. for Addiction and Mental Hlth., Toronto, ON, Canada; [6]Biol. Sci., [5]Univ. of Toronto Scarborough, Toronto, ON, Canada

**Abstract:** Alzheimer’s disease (AD) impacts over 55 million people worldwide according to the World Health Organization. Canonical hallmarks include amyloid-β plaques and neurofibrillary tangles, but people living with AD also have other biochemical changes including elevated neuroinflammation and oxidative stress inducing protein damage, and autophagic deficits increasing the accumulation of aberrant proteins. Subsequent neurodegeneration in the cortex and hippocampus leads to the eventual cognitive decline observed in AD patients. AD development and progression is a multi-factorial process and knowledge gaps limit our ability to effectively halt disease progression. Risk factors can include anxiety/depression and sleep disruption, and preliminary work from our lab has demonstrated that sleep disruption-associated

autophagic impairments precede cognitive decline in an AD mouse model. Consequently, this project examines the link between chronic sleep disruption and anxiety-like behaviours on cognition, proteostasis, and neurodegeneration in mouse models of AD pathology. Chronic stress response is induced using unpredictable aversive light and high-frequency tones over 2-weeks causing sleep disruption in 6-month-old human amyloid precursor protein knock-in mice. Following this, we assess home-cage behaviour, cognition, and stress, followed by biochemical and immunohistochemical analyses of their brains. Significant sex differences were observed in a home-cage assessment with sleep-disrupted females sleeping significantly more during the dark cycle, when mice are typically active, while males were unaffected. Overall, mice slept more over the first 24-hour period following sleep-disruption and built better nests after 18 hours compared to non-sleep-disrupted control mice. Our sleep disruption paradigm resulted in trends for male-specific enhancements in exploratory activity and increases in anxiety-like behaviours. Finally, elevated levels of the autophagic flux and protein aggregate marker, P62, in the hippocampus of female mice indicated that autophagy disruptions and proteinopathy may be promoted with chronic-sleep disruption. Similarly, preliminary data indicates that sleep-disrupted human tau knock-in mice may have altered home cage and anxiety-like behaviours ameliorated by the anti-insomnia drug suvorexant. By delving deeper into the impact of chronic sleep disruption on cognitive abilities, stress levels, and proteostasis, we can enhance our understanding of AD development and potentially uncover a novel target for drug development that could halt AD progression.

**Disclosures: D. Wear:** None. **C.D. Morrone:** None. **D. Simpson:** None. **F. Azhar:** None. **A. Seregin:** None. **R. Alam:** None. **H. Yu:** None.

**Poster**

**PSTR012. APP/Abeta Pathway: Cellular and Animal Models I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR012.13/Web Only

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

**Support:** CIHR PJT-169197

**Title:** L-type calcium channel mediates pre-tangle tau-induced neuronal degeneration in the locus coeruleus: a pilot study

**Authors: *T. OMOLUABI**, J. PICHE, Z. HASSAN, C. A. CROSSLEY, Q. YUAN; Biomed. Sci., Mem. Univ. of Newfoundland, St. John's, NL, Canada

**Abstract:** Neuronal decline associated with aging is evident in many neurodegenerative diseases, including Alzheimer’s disease (AD). Neurons rely on mitochondria ATP to maintain ionic gradients and generate axonal and synaptic membrane potentials. Alteration of synaptic plasticity and cognitive decline in aging and AD is linked to dysregulation of calcium ions ($Ca2^{+}$). In the calcium hypothesis of aging and AD, increased cytosolic $Ca2^{+}$ via L-type calcium

channels (LTCC) could lead to mitochondrial dysfunction and neuronal degeneration. Mitochondria contribute to intracellular $Ca2^{+}$ signaling, and proper $Ca2^{+}$ levels in the mitochondrial matrix regulate oxidative phosphorylation activity, which maintains the rate of ATP production. In this work, we study the role of LTCCs in pre-tangle tau (soluble precursor of neurofibrillary tangles) pathology in a rat model. The earliest abnormality associated with AD is the presence of pre-tangle tau in the noradrenergic locus coeruleus (LC) neurons. Pre-tangle tau is first seen in neurons of the LC and spreads to other brain regions. We have previously shown that pre-tangle tau in the rat LC impaired memory and cognition, paralleled by fiber degeneration and cell loss, implicating that the neuronal health of the LC is vital in brain health. However, how pre-tangle tau affects LC neuronal health is unknown. In this study, we hypothesize that LC neuronal health impairment by pre-tangle tau results from LTCC-mediated $Ca2^{+}$-mitochondria dysregulation. We infused a pseudophosphorylated human tau gene in the LC of 2-5 or over 12-month-old tyrosine hydroxylase-Cre rats. Control rats received virus infusion except for the absence of the pre-tangle gene in the control virus. Seven months post-virus infusion, an LTCC antagonist, nimodipine, was administered intraperitoneally for six weeks. Rats were later exposed to batteries of behavioral tests to index memory and cognitive function. The preliminary result showed that pre-tangle tau elevates LTCC, and chronic nimodipine administration rescued spatial and olfactory behavioral deficiencies induced by pre-tangle tau. Our data support the involvement of $Ca2^{+}$ in AD and suggest that therapeutics targeted at the LTCC-mitochondria-LC pathway could be beneficial in AD intervention.

**Disclosures: T. Omoluabi:** None. **J. Piche:** None. **Z. Hassan:** None. **C.A. Crossley:** None. **Q. Yuan:** None.

**Poster**

**PSTR012. APP/Abeta Pathway: Cellular and Animal Models I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR012.14/E8

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

**Support:** NIH Grant NS085171 (JC)
NIH Grant AG065290 (JC)
Supported by a grant from the American Epilepsy Society (MSP)

**Title:** Enhancing noradrenergic tone decreases epileptiform activity in amyloid precursor protein transgenic mice

**Authors: *M. SILVA-PÉREZ**, J. PARK, J. CHIN;
Neurosci., Baylor Col. of Med., Houston, TX

**Abstract:** Individuals with Alzheimer’s disease (AD) have an increased incidence of epilepsy, which is often underestimated due to the prevalence of non-convulsive seizures and their preferential occurrence during sleep. Several transgenic mouse lines that express human amyloid

precursor protein (APP) carrying AD-linked mutations also exhibit epileptiform activity primarily during sleep. We found that APP mice from line J20 exhibit epileptiform spikes that are most frequent during rapid eye movement (REM) sleep at early stages of disease and become more abundant during nonrapid eye movement (NREM) sleep with age and disease progression. The mechanisms that underlie the increased susceptibility to epileptiform activity during sleep and the age-related shift in incidence of epileptiform spikes are unclear. Norepinephrine, a neuromodulator reported to have antiepileptic effects, exhibits a pattern that is opposite of AD-related epileptiform activity: norepinephrine abundance is low during sleep and high during wakefulness. We hypothesized that norepinephrine dynamics could explain the preferential occurrence of epileptiform activity during sleep, and that a gradual dysfunction of norepinephrine neurotransmission may underlie the age-related increase in incidence of epileptiform spikes during NREM sleep. To investigate whether AD-related epileptiform activity is indeed modulated by norepinephrine, we enhanced norepinephrine tone through treatment with reuptake inhibitors or chemogenetic stimulation of the locus coeruleus in female and male APP mice implanted with electrodes for chronic EEG recordings. Epileptiform spikes were quantified and sleep scoring was performed to assess epileptiform spike rates across the sleep-wake cycle. Both the treatment with norepinephrine reuptake inhibitors and the chemogenetic stimulation of the locus coeruleus led to acute and reversible decreases in spike abundance, especially during NREM sleep. Effects were most pronounced shortly after administration and gradually subsided over the course of several hours. These results demonstrate that norepinephrine levels influence the abundance of epileptiform activity in APP mice, and suggest that enhancing norepinephrine tone may be a compelling therapeutic avenue in the context of AD-related epilepsy.

**Disclosures:** **M. Silva-Pérez:** None. **J. Park:** None. **J. Chin:** None.

**Poster**

**PSTR012. APP/Abeta Pathway: Cellular and Animal Models I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR012.15/E9

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

**Support:** NIH Grant 5R01NS100919

**Title:** Oxidative DNA damage-mediated transcriptional mutagenesis of APP and its contribution to Alzheimer's disease.

**Authors: *I. JEONG**, W. BAE, A. KONERU, Y.-S. KIM;
Inst. for Neurolog. Therapeut., Rutgers, The State Univ. of New Jersey, Piscataway, NJ

**Abstract:** 8-Oxo-2'-deoxyguanosine (8-oxodG) is the most frequent oxidative stress-induced DNA lesion and is commonly associated with neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson’s disease (PD) as well as aging process. The accumulation of 8-oxodG in non-dividing cells, such as the neurons, has been shown to induce transcriptional

mutagenesis (TM), but its contribution to neurodegenerative conditions yet to be elucidated. Our recent study demonstrates that novel mutant mRNA species of alpha-synuclein generated by the TM process could lead to PD pathogenesis. This interesting finding prompts us to investigate if 8-oxodG-mediated TM could similarly contribute to AD. Here we investigate whether8-oxodG accumulation results in TM-mediated novel Amyloid precursor protein (APP) mRNA mutant species that yield amyloid-beta (Aβ) accumulation using both cell culture and mice models. To achieve 8-oxodG accumulation, we first established 8-oxoguanine DNA glycosylase-1 (OGG1) knock down in ReN VM, human neuronal progenitor cells and employed Ogg1 KO mice. Under oxidative stress conditions, inhibition of OGG1 resulted in increased nuclear accumulation of 8-oxodG. It has been reported that Aβ42 treatment causes oxidative stress. To determine 8-oxodG levels, differentiated ReN VM was treated with Aβ42. Following treatment with Aβ42 oligomers for 24 hours, a significant increase in nuclear 8-oxodG levels, approximately 1.8-fold higher ($p$=0.0181), was observed in the OGG1 KD cells treated with 5μM Aβ42 compared to the control condition. Hippocampal injection of Aβ42 similarly increased 8-oxodG accumulation in Ogg1 KO mice. Next, we analyzed the region of APP containing Aβ (between amino acid (aa) 670 and 724; Aβ1-42, aa 672-713) where all known pathogenic APP mutations causing familial AD (fAD) are found, predicting total 16 TM-derived missense mutations within this region. Among them are TM variants, A713E, T714K, T719N, and L723M, that are located in the transmembrane domain and predicted to readily generate Aβ42. We established ReN VM stably expressing each TM variant and found that T719N exhibits significant increase in Aβ42 compared to WT using ELISA, confirming that APP TM variants potentially contribute amyloid pathology. Overall, this study highlights the significance of novel APP TM in AD pathogenesis mediated by 8-oxodG. Furthermore, it is anticipated that this research will serve as a fundamental understanding of the underlying mechanisms and the development of therapeutic approaches of AD in the future.

**Disclosures: I. Jeong:** None. **W. Bae:** None. **A. Koneru:** None. **Y. Kim:** None.

**Poster**

**PSTR012. APP/Abeta Pathway: Cellular and Animal Models I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR012.16/E10

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

**Support:** R01AG067048

**Title:** Disrupted mitochondrial response to nutrients is an early signature in the APP Knock-In mice

**Authors: *A. NORAMBUENA**[1], P. RAUT[2], Z. WANG[5], V. SAGAR[2], H. WALLRABE[2], E. C. PARDO[3], S. HU[5], A. PERIASAMY[2], G. S. BLOOM[4];
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**Abstract:** Mitochondrial dysfunction, oxidative stress and mTOR dysregulation occur in neurodegenerative disorders like Alzheimer's disease (AD), but how these processes mechanistically promote neurodegeneration is still poorly understood. We recently discovered 'Nutrient-induced Mitochondrial Activity' (NiMA), an inter-organelle signaling pathway whereby amino acid stimulation of lysosomal mTORC1 regulates oxidative phosphorylation and mtDNA synthesis in perikaryal mitochondria in neurons in culture. We also reported NiMA to be negatively regulated by extracellular amyloid-β oligomers (xcAβOs; Norambuena, et al. 2018. *EMBO J* 37: e100241). The mechanism involves xcAβO activation of mTORC1 at the neuronal plasma membrane (Norambuena, et al. 2017. *Alzheimers Dement* 13: 152-167) and its associated inhibition at lysosomes. The latter leads to upregulation of superoxide dismutase 1, a major regulator of cellular redox (SOD1; Norambuena, et al. 2022. Neurobiol Dis. doi: 10.1016/j.nbd.2022.105737). We now report NiMA inhibition in live brain by a mechanism involving the GSK3β-mTORC1-SOD1 signaling pathway. By tracking mitochondrial metabolism in APP knock-in mouse brain (APPKI; Jackson Lab) with two-photon fluorescence lifetime imaging of NAD(P)H and multi-parametric photoacoustic microscopy, we found NiMA to be downregulated in 4-month-old APPKI mice and completely blocked in 6-month-old animals. Disruption of NiMA, thus occurs ~2-3 month before cognitive decline and other pathological AD features detected in this amyloid-β mouse model. Mechanistically, we found that GSK3β signals through mTORC1 to regulate SOD1 and mitochondrial activity. Pharmacological inhibition of GSK3β in 4-month-old APPKI mice partially restored mitochondrial functioning. These observations suggest that the GSK3β-mediated regulation of NiMA may control SOD1's ability to interact with cytosolic regulators. Proximity-dependent biotin identification assays followed by mass spectrometry identified PDE4D5 as a potential $SOD1_{pT40}$-dependent interacting partner. Also, a lentiviral-mediated shRNA screen targeting 96 mTOR substrates was performed to seek regulators of the NiMA pathway in NPC-derived human neurons. Seventeen mTOR substrates were found to regulate NiMA, including AKAP1, a major mitochondrial regulator of PKA activity. Thus, we are unveiling a fundamental mechanism connecting nutrient sensing, mTORC1 kinase activity, cytosolic redox regulation and PKA activity to perikaryal mitochondrial functioning in mammalian neurons. Also, our results suggest that NiMA disruption is an early event in AD pathogenesis.

**Disclosures:** **A. Norambuena:** None. **P. Raut:** None. **Z. Wang:** None. **V. Sagar:** None. **H. Wallrabe:** None. **E.C. Pardo:** None. **S. Hu:** None. **A. Periasamy:** None. **G.S. Bloom:** None.

**Poster**

**PSTR012. APP/Abeta Pathway: Cellular and Animal Models I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR012.17/Web Only

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

**Support:** CIHR PJT-169197

**Title:** Enhancing noradrenergic activity using Atomoxetine improves olfactory discrimination learning in rats.

**Authors: *R. ABU-LABDEH**, T. OMOLUABI, Q. YUAN;
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**Abstract:** The locus coeruleus (LC) experiences a critical loss of neurons throughout the progression of Alzheimer's disease (AD). The LC is the primary source of norepinephrine (NE) in the brain, increasing NE transmission has been suggested to delay AD pathogenesis. There are two distinct firing patterns of LC neurons, phasic which occur when exposed to novelty, and tonic. Previous work conducted in our lab demonstrated that phasic LC neuron activity aids in learning and memory. Meanwhile high tonic firing results in the increase of stress indicators in rodents. Furthermore, phasic, but not tonic, chronic optogenetic LC activation has been shown to prevent neurotoxicity and cognitive impairment in an LC pretangle tau model. For therapeutic purposes, it is important to investigate the effects of LC phasic activation using non-invasive approaches. Here we test the effect of Atomoxetine (ATM), an FDA-approved norepinephrine (NE) transporter inhibitor for olfactory functions in wild-type rats. ATM enhances the phasic-to-tonic signal ratio in the LC and may be a useful candidate to test the therapeutic effect of regulating LC-NE circuitry in AD. Rats were observed in an odour discrimination learning task where they learned to discriminate against odours with a reward. The lowest concentration of an odour to trigger a sniffing behaviour was measured, this is known as the odour detection threshold. We compared the performance of aged vs. young rats as well as the ATM dose of 0.3 mg/kg vs 1 mg/kg vs. vehicle-injected rats. Preliminary results indicate no age-related decline in odour discrimination and ATM in a dose of 1mg/kg significantly improved odour discrimination in adult rats. The threshold to detect the reward-trained odour and a novel odour was not altered by ATM. This study highlights the potential of ATM as a therapeutic intervention for AD by targeting the LC and enhancing NE transmission. As olfactory deficits are one of the earliest signs of AD, the improvement of odour discrimination learning by ATM has an implication for alleviating olfactory and other cognitive deficits in AD.

**Disclosures:** **R. Abu-Labdeh:** None. **T. Omoluabi:** None. **Q. Yuan:** None.

**Poster**

**PSTR012. APP/Abeta Pathway: Cellular and Animal Models I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR012.18/E11

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

**Support:** RS-2023-00208475
RS-2023-00244920
SNU BK21 Four

**Title:** High glucose impairs neuronal Aβ degradation through TRIM16-mediated lysophagy defects

**Authors: *C. CHAE**, *C. CHAE, J. YOON, J. CHO, H. HAN;
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**Abstract:** Although lysosomal dysfunction is a pathogenic connection that may explain the causative linkage between diabetes and Alzheimer's disease, there is no evidence on how the regulation of hyperglycemia in neuronal lysophagy modifies lysosomal function. Here, we aim to determine the effect and regulatory mechanisms of high glucose-suppressed lysophagy on neuronal Aβ accumulation and cognitive impairment. We have used human induced-pluripotent stem cell (hiPSC)-derived neurons, mouse hippocampal neurons, and SH-SY5Ys ($n$ = 5) exposed to high glucose, immunofluorescence assay, and electron microscopy to identify the underlying mechanisms. Streptozotocin-induced diabetic mice ($n$ = 5) and behavior test were used to elucidate whether the lysophagy contributes to cogntivie impairment. We find that by causing lysosomal membrane permeabilization due to reactive oxygen species and impairing lysophagy, high glucose induces neuronal lysosomal dysfunction. With regard to lysophagy-related factors, AMPK-mammalian target of rapamycin complex 1 (MTORC1)-mediated suppression of transcription factor EB (TFEB) activity downregulates tripartite motif containing 16 (TRIM16) expression both in neuronal cells exposed to high glucose and in the hippocampus of diabetic mice. pcDNA3.1-Trim16 transfection restores neuronal lysophagy through the recruitment of ubiquitin, p62, and microtubule-associated protein 1A/1B-light chain 3 to damaged lysosomes, which blocked the high glucose-accumulated Aβ and phosphorylated tau. Pharmacological enhancement of TFEB improves cognitive impairment in diabetic mice by restoring hippocampal lysophagy. These results suggest that through TRIM16-mediated lysophagy deficiencies, high glucose inhibits neuronal Aβ degradation. Taken together, a potential strategy for the prevention of diabetes-related Alzheimer's disease pathogenesis is to modulate TRIM16-mediated lysophagy.

**Disclosures:** **C. Chae:** None. **C. Chae:** None. **J. Yoon:** None. **J. Cho:** None. **H. Han:** None.

**Poster**

**PSTR012. APP/Abeta Pathway: Cellular and Animal Models I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR012.19/E12

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

**Support:** NIH Grant 5R01NS128467-02
NIH Grant R01AG064226

**Title:** Pyroglutamate Aβ interactome in the brain of TgF344-AD rat model of Alzheimer's disease

**Authors: *T. TITTLE**[1], S. CHOI[1], K. HAUSER[2], B. KILLINGER[1], L. ROMANOVA[1]; [1]Neurolog. Sci., Rush Univ. Grad. Col., Chicago, IL; [2]ASU-Banner Neurodegenerative Dis. Res. Ctr. (NDRC), Arizona State Univ., Tempe, AZ

**Abstract:** Alzheimer's disease (AD) is a complex neurodegenerative disease that involves the accumulation of β-amyloid (Aβ) and tau in the brain. Recently, several therapeutic antibodies have been developed including donanemab which target a specific form of Aβ, pyroglutamate-Aβ (pE3-Aβ), a highly toxic, aggregation-prone derivative of Aβ. pE3-Aβ is gaining attention as a potential key player in AD pathology and a promising therapeutic target, but its specific role for AD pathogenesis remains poorly understood. The goal for this study was to identify spatial interactomes for Aβ and pE3-Aβ to better understand their role in the precipitation of amyloid pathology in the brain. Here, we determined the interactome of Aβ and pE3- Aβ in the brain of 70-week-old transgenic rats (TgF344-AD) using in situ proximity labeling method called biotinylation by antibody recognition (BAR). TgF344-AD rats co-express mutant human presenilin 1 (PS1ΔE9) and mutant human amyloid precursor protein ($APP_{sw}$). Anti-Aβ antibodies 4G8, 6E10, and anti- pE3-Aβ antibody D5N5H were used to BAR label total Aβ and pyroglutamate Aβ, respectively. BAR-labeled proteins were purified and identified via liquid chromatography-tandem mass spectrometry (LC-MS/MS). Pathology was characterized by immunohistochemistry (IHC) and immunofluorescence multiplexing. IHC characterization revealed widespread Aβ plaques across the neuroaxis of TgF344-AD rats. Antibodies 4G8 and 6E10 labeling was less specific for plaques, as we saw appreciable staining in the apparent neurons of TgF344-AD rats and, to a lesser extent, staining in wild-type (WT) rats. In contrast, anti- pE3-Aβ antibody, D5N5H, showed high specificity for plaques, with no observable staining in apparent neurons or the WT rat brain. Tau pathology was minimal, with spurious immunoreactive tangles observed in the hippocampus of TgF344-AD rats. Subsequent LC-MS/MS of BAR labeled fractions revealed many enriched proteins for capture antibodies 4G8, 6E10, and D5N5H in the brain. Analysis of BAR data showed that 4G8 and 6E10 interactomes are very similar to one another but distinct from pE3-Aβ interacting proteins. These results point to the special role of pE3-Aβ in the formation of Aβ plaques. Top hits identified for pE3-Aβ interactions were APOE, CLU, and APP (i.e., target protein), which are known participants in AD pathogenesis. Anti-pE3-Aβ antibody D5N5H specifically labeled plaques in the brain of TgF344-AD rats. BAR-D5N5H identified three pE3-Aβ interacting proteins, all well-described AD risk genes. Future studies should focus on functional interactions between APOE, CLU, and pE3-Aβ.

**Disclosures: T. Tittle:** None. **S. Choi:** None. **K. Hauser:** None. **B. Killinger:** None. **L. Romanova:** None.

**Poster**

**PSTR012. APP/Abeta Pathway: Cellular and Animal Models I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR012.20/E13

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

**Support:** NIH Grant 1RF1NS127413

**Title:** Ischemic stroke accelerates emergence of dementia-like symptoms in the App/PS1 Alzheimer's mice

**Authors: *T. D. APOLINARIO**, C. M. ANDERSON, C. E. BRAY, J. G. POTT, A. L. TORRES, J. E. ORFILA, P. S. HERSON;
Neurolog. Surgery, Ohio State Univ., Columbus, OH

**Abstract:** Ischemic strokes are considered a leading cause of death and disability worldwide, with increasing evidence for post-stroke cognitive impairment (PSCI). An emerging hypothesis relates to PSCI and Alzheimer's disease (AD) sharing common pathologies across all age groups. This converging pathology lead us to investigate if being genetically pre-disposed to AD would accelerate cognitive disfunctions following a stroke. We hypothesize that Alzheimer's-predisposed (APP/PS1 positive) mice expressing amyloid beta proteins at a pre-symptomatic age show cognitive disfunction following ischemic stroke. This study used electrophysiology and behavior to assess memory impairments following a 30min Middle Cerebral Artery Occlusion (MCAO) stroke. To assess the effect of stroke on hippocampal long-term potentiation (LTP), a well-accepted cellular model of learning and memory, extracellular field recordings of sch-CA1 neurons were performed in acute hippocampal slices prepared 30 days after MCAO in both APP/PS1 expressing and littermate wildtype control mice. Under control conditions, a physiological theta burst stimulation (40 pulses, 100Hz) resulted in LTP that increased the slope of fEPSP to 192.3% ± 15.39 (n=6) of baseline. However, APP/PS1 expressing MCAO mice showed impaired LTP (143.2% ± 13.89, n=5, $p<0.05$). While behavioral studies are currently ongoing, we are hopeful these data will further confirm our hypothesis that being genetically pre-disposed to AD can increase the likelihood of developing AD following stroke.

**Disclosures: T.D. Apolinario:** None. **C.M. Anderson:** None. **C.E. Bray:** None. **J.G. Pott:** None. **A.L. Torres:** None. **J.E. Orfila:** None. **P.S. Herson:** None.

**Poster**

**PSTR012. APP/Abeta Pathway: Cellular and Animal Models I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR012.21/E14

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

**Support:** AMED JP211m0203078
AMED JP20dm0107142
a Grants-in-Aid for Scientific Research 23K06840

**Title:** Peripherally administered p3-Alcβ9-19 peptide restored neuronal viability and reduced neuroinflammation in the brain of AD mouse models

**Authors: *T. SUZUKI**;
Hokkaido Univ., Sapporo-Shi, Japan

**Abstract:** In the brain of aged subjects with Alzheimer's disease (AD), amyloid β (Aβ) accumulates and forms neurotoxic oligomers (Aβo) and fibrils, which impair neuronal viability and evoke inflammation. This pathogenic process is believed to be the primary cause of neurodegeneration, resulting in cognitive deficits and memory loss. We have shown that p3-Alcβ peptides are generated from neuronal precursor Alcadein β/Clstn3 in a similar fashion to Aβ generation (Hata *et al*., 2009). We found that p3-Alcβ enhanced the mitochondrial activities of neurons and protected the neurons against Aβo-induced toxicity. In this study, we examined the ability of p3-Alcβ to preserve neuronal health against Aβ toxicity in vivo. **[Procedures]** Functionally active 11-amino acid peptide, p3-Alcβ9-19, of p3-Alcβ37 (a major p3-Alcβ of 37-amino acid) was injected subcutaneously in AD mice ($App^{NL\text{-}F/NL\text{-}F}$). Successful transfer of p3-Alcβ9-19 into the cerebrospinal fluid (CSF) was confirmed with a specific sELISA. Neuronal viability was investigated by monitoring brain mitochondrial function using PET imaging with a [$^{18}$F]BCPP-EF probe which detects mitochondrial complex I activity. The level of neuroinflammation was assessed in parallel with PET imaging using [$^{11}$C]DPA713, a TSPO PET radiotracer. **[Results]** AD mice showed a significant decrease in [$^{18}$F]BCPP-EF SUVR in the cortex and hippocampus compared with age-matched wild-type (WT) mice. Interestingly, SUVR values in AD mice were restored to levels in WT mice after a single injection of p3-Alcβ9-19 (1mg/kg weight). In AD mice, SUVRs of [$^{11}$C]DPA713 showed a significant inverse correlation with those of [$^{18}$F]BCPP-EF in vehicle injections. This inverse correlation changed to a positive correlation with a single injection of p3-Alcβ9-19. **[Conclusion]** Mitochondrial impairment which decreases survival in neurons is associated with an increase in neuroinflammation evoked by Aβ burden in AD mice. Administration of p3-Alcβ9-19 showed the neuroprotective property against Aβo toxicity in vivo. **[Discussion]** The administration of p3-Alcβ9-19 may be a promising treatment for restoring and protecting brain function in early AD patients who show lower endogenous p3-Alcβ37 levels in CSF compared to those in age-matched nondemented subjects.

**Disclosures: T. Suzuki:** None.

**Poster**

**PSTR012. APP/Abeta Pathway: Cellular and Animal Models I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR012.22/E15

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** National Key R&D Program of China (2021YFE0203000)
Research Grants Council of Hong Kong (the Theme-Based Research Scheme [T13-605/18W])
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Innovation and Technology Commission (InnoHK and ITCPD/17-9)
the Guangdong Provincial Key S&T Program Grant (2018B030336001)
Guangdong Provincial Fund for Basic and Applied Basic Research (2019B1515130004)

**Title:** A herbal formula enhances synaptic plasticity in Alzheimer's disease model mouse

**Authors: *F. C. F. IP**[1,2,3], L. OUYANG[1], E. Y. L. CHENG[1], K. C. LOK[2], Y. B. JIANG[2], J. S. C. WONG[2], H. K. KOON[2], G. M. FU[2], J. K. Y. LAU[1], W. Y. FU[2], N. Y. IP[1,2,3];
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**Abstract:** Alzheimer’s disease (AD), the most common aging-related neurodegenerative disorder, is clinically characterized by progressive memory loss and other life-limiting cognitive impairments. Current treatments mainly provide transient symptomatic relief, highlighting the pressing need for effective anti-AD drugs and early intervention. Here, we leveraged the longstanding history of herbal decoctions used in traditional Chinese medicine for the treatment of cognitive symptoms to investigate the effects of an herb pair named *Tiansi Yin* (TSY) on memory function. TSY treatment via daily oral gavage for 28 weeks enhanced the behavioral performance of aged C57BL/6 mice in the exploratory open-field test. TSY treatment also enhanced synaptic functions in both young adult and aged mice, as reflected by increased long-term potentiation. These findings are concordant with the traditional use of TSY for the treatment of memory loss. Moreover, TSY administration in the APP/PS1 transgenic mouse model of AD significantly reversed the long-term potentiation deficits in both young and aged mice. Furthermore, in cultured hippocampal neurons, TSY treatment promoted dendritic spine density and the expression of pre- and postsynaptic proteins crucial for synaptic functions (i.e., VGluT1 and PSD95) while facilitating excitatory neurotransmission. Corresponding proteomic analysis of these neurons also suggests that TSY mediates neuroprotective effects on synaptic plasticity at the molecular level. These findings collectively suggest that TSY functions to support synaptic functions and enhance memory performance.

**Disclosures:** **F.C.F. Ip:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Infitech. **L. Ouyang:** None. **E.Y.L. Cheng:** None. **K.C. Lok:** None. **Y.B. Jiang:** None. **J.S.C. Wong:** None. **H.K. Koon:** None. **G.M. Fu:** None. **J.K.Y. Lau:** None. **W.Y. Fu:** None. **N.Y. Ip:** None.

**Poster**

**PSTR013. Tau: Aggregation and Phosphorylation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR013.01/E16

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

**Support:** BrightFocus Foundation

**Title:** Uncovering Novel Modifiers of Tau Aggregation and Pathology using a Proximity Proteomics Approach (BioID)

**Authors: *J. H. LEE**[1,3], D. MORDERER[2], M. C. WREN[2], B. KHALIL[2], C. L. SMITH[2], C. L. CROFT[4], Y. CARLOMAGNO[2], A. M. LY[2], F. LIU[2], C.-W. TSAI[2], M. R. SALEMI[5], M. DETURE[2], D. W. DICKSON[2], B. PHINNEY[6,5], C. N. COOK[2], T. E. GOLDE[7], L. PETRUCELLI[2], W. ROSSOLL[2];
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**Abstract: Background:** Neurofibrillary tangles (NFTs), a defining hallmark of AD and other tauopathies, are formed by the aggregation of the microtubule-associated protein tau into pathological oligomers and fibrils. Although NFTs are believed to play a pivotal role in the disease process, we have a poor understanding of how their formation, toxicity, and spread across brain regions is regulated. Recent data suggest that tau seeding behavior is governed by patterns of posttranslational modifications and varying filament structures. Understanding how tau-associated proteins regulate the oligomerization, pathological accumulation, and seeding of tau in affected neurons and glia is of critical importance for AD therapy development.
**Method**: We have established novel proximity-dependent biotin-identification (BioID) approaches to identify the composition and proximal molecular environment of insoluble protein aggregates in cells and brain tissue. Using an *in vitro* and *ex vivo* model approach coupled with mass spectrometry, we identified proteins enriched in proximity to hyperphosphorylated tau aggregates, assessed its endogenous and overexpression in its interactions with tau and validated their expression levels with NFTs in the context of human AD pathology. To study its functional relationship with tau, we utilized a tau seeding model and observed its impact on tau aggregate formation and toxicity.
**Result**: To determine the physiological and aggregate specific interacting partners of tau, we are comparing wild type tau with mutant tau carrying three tauopathy-associated mutations (A152T/P301L/S320F) that form hyper-phosphorylated and thioflavin S-positive aggregates. The proteomic analysis from our combined proteomic datasets revealed that proteins significantly enriched with mutant vs. wild-type tau include candidates involved in RNA processing, as well as protein ubiquitination and proteasome degradation. Our validation experiments revealed that a key protein is present specifically in NFTs in human AD and primary tauopathy brain tissue. We also confirmed co-localization of this protein in tau aggregates in our tau seeding model, allowing us to test and assess its druggable potential for tauopathies.
**Conclusion:** We have identified a key protein that interact with different stages of tau in the disease process, giving us insight into the therapeutic window of opportunity in NFT development. Further confirmation of this protein in a tau seeding model will allow us to test how they mediate the toxic effect of NFTs, facilitate the formation of pathological tau aggregates and prevent the aberrant phase transition of tau into pathological fibrils.

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**Poster**

**PSTR013. Tau: Aggregation and Phosphorylation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR013.02/E17

**Topic:** C.02. Alzheimer"s Disease and Other Dementias

**Support:** Alzheimer's Association (AA) Grant AARF-22-722571
NIH/NIA Grant U19AG074879
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NIH/NIA Grant U01 AG068057

**Title:** Spatial transcriptomic patterns underlying regional vulnerability to amyloid-β and tau pathologies and their relationships to cognitive dysfunction in Alzheimer's disease

**Authors: *M. YU**[1], S. L. RISACHER[2], O. SPORNS[3], A. J. SAYKIN[2];
[1]Indiana University-Purdue Univ. Indianapolis, Indianapolis, IN; [2]Indiana Univ. Sch. of Med., Indiana Univ. Sch. of Med., Indianapolis, IN; [3]Olaf Sporns, Indiana Univ., Bloomington, IN

**Abstract:** Amyloid-β (Aβ) and tau proteins accumulate within distinct neuronal systems in Alzheimer's disease (AD). Although it isn't clear why certain brain regions are more vulnerable to Aβ and tau pathologies than others, gene expression may play role. We studied the association between brain-wide gene expression profiles and regional vulnerability to Aβ (gene-to-Aβ associations) and tau (gene-to-tau associations) pathologies leveraging two large independent cohorts (n = 715) of participants along the AD continuum. We identified several AD susceptibility genes and gene modules in a gene co-expression network with expression profiles related to regional vulnerability to Aβ and tau pathologies in AD. In addition, we identified distinct biochemical pathways associated with the gene-to-Aβ and the gene-to-tau associations. These findings highlight the distinct genetic contribution to the vulnerability of specific brain regions to Aβ and tau pathologies. Finally, we propose a novel analytic framework, linking the identified gene-to-pathology associations with cognitive dysfunction in AD, to facilitate the translation of gene-to-pathology associations to clinical utility.

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**Poster**

**PSTR013. Tau: Aggregation and Phosphorylation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR013.03/E18

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

**Support:** NIH Grant 1RF1AG076122-01A1
Chang-Zuckerberg Initiative Collaborative Pairs Pilot Project Award

**Title:** In Situ Proteomic Profiling of Phospho-Tau Pathology in Alzheimer's Disease and Primary Tauopathies

**Authors: *D. MORDERER**[1], M. C. WREN[1], F. LIU[1], N. KOURI[1], B. KHALIL[1], M. R. SALEMI[2], D. W. DICKSON[1], B. S. PHINNEY[2], M. E. MURRAY[1], W. ROSSOLL[1];
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**Abstract:** Pathological aggregation of hyperphosphorylated protein tau in brain is a hallmark of a group of neurodegenerative diseases known as tauopathies that currently include over 25 diseases. Different tauopathies are characterized by specific types of tau lesions present in affected brain areas. These lesions include neurofibrillary tangles, Pick bodies, neuropil threads, neuritic plaques, or astrocytic plaques. Recent studies have demonstrated that tau filaments isolated from different tauopathies have distinct structures that potentially underlines morphological diversity of tau lesions. Factors that modulate structural diversity of pathological tau species or mediate their neurotoxic effects remain poorly understood, highlighting the importance of studying proteomes associated with different tau aggregate types. In this study we utilized an in situ probe-dependent proximity profiling (ProPPr) approach to identify the proteomes associated with phospho-tau aggregates in Alzheimer's disease (AD), corticobasal degeneration (CBD), and Pick's disease (PiD) cases in formalin-fixed paraffin-embedded (FFPE) frontal cortex sections from the Mayo Clinic Florida brain bank. We have identified over 1000 proteins associated with phospho-tau aggregates in frontal cortices. 228 proteins were associated with phospho-tau in all diseases. Analysis of protein-protein interaction network for this protein set revealed presence of several clusters of functionally related proteins. Most notable clusters included chaperones, cell adhesion molecules, proteins involved in vesicle transport and energy metabolism. Analysis of protein differential abundance between conditions revealed set of proteins with altered association with phospho-tau aggregates in different tauopathies. Overall**,** the proposed *in situ* ProPPr method optimized in our lab can be successfully used for characterization of neuropathologic aggregate-associated proteomes using archived FFPE tissue.

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**Poster**

**PSTR013. Tau: Aggregation and Phosphorylation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR013.04/E19

**Topic:**

**Support:** AARF-22-972333
T32AG000255
R01AG077692

**Title:** Seizures enhance the spread of pathological tau in an Alzheimer's Disease mouse model

**Authors: *K. HOAG**[1], A. BARBOUR[2], X. LI[2], S. ZEBROWITZ[2], C. HASSMAN[2], V. M. Y. LEE[3], D. M. TALOS[2], F. E. JENSEN[2];
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**Abstract:** Up to 64% of people with Alzheimer's Disease (AD) also experience seizures which we and others have shown is associated with worsened cognitive and pathological outcomes. Recent data suggest that through neuronal activity, pathological hyperphosphorylated (p)-tau can spread transsynaptically, transmitting p-tau to the postsynaptic neuron. In the context of AD, the spread of p-tau is correlated with cognitive decline. Given that tau can be spread through the brain via neuronal activity, we hypothesized that seizure-related hyperactivity would enhance the spread of p-tau and exacerbate cognitive decline. To model tau spread we injected human AD-derived tau (AD-tau, 2 µg total) into the right hippocampus and the overlying cortex of a novel cross between the Five times familial AD (5XFAD) model and a Fos driven targeted recombination in active populations (FosTRAP) mouse line (5X-TRAP). 5X-TRAP mice and their littermates, control WT-TRAP mice, underwent AD-tau injection at 3 months of age, followed by an established pentylenetetrazol (PTZ) kindling protocol to induce seizures starting at 2-3 weeks post-injection. The 5X-/WT-TRAP mice allowed for permanent labelling of Fos+ cells that were activated during seizures to quantify seizure-induced neuronal activity. At 3 months following AD-tau injection, mice underwent cognitive testing and were subsequently euthanized for p-tau AT8 [Ser202; Thr205] immunohistochemistry (IHC). During the kindling protocol, on average, 5X-TRAP mice developed tonic-clonic seizures quicker than their WT-TRAP counterparts ($p=0.059$) and had more seizure-induced neuronal activation (TRAP-labelled) in the dentate gyrus (DG) ($p<0.05$) suggesting that 5X-TRAP mice are more susceptible to seizures. In addition, a genotype x kindling interaction revealed that PTZ-treated 5X-TRAP mice performed worse on novel object recognition compared to saline administered 5X-TRAP mice ($p<0.05$). IHC revealed that AD-tau seeded 5X-TRAP mice that received PTZ had significantly elevated AT8 coverage in the DG and CA1 of the hippocampus contralateral to the injection site when compared to 5X-TRAP mice who received saline ($p<0.05$). Further, in the ipsilateral hippocampus, there was a trend towards increased AT8 coverage in the DG across kindled groups ($p=0.083$) and 5X-TRAP mice displayed increased AT8 coverage in the CA1 compared to WT-TRAP ($p<0.05$). Overall, we found that seizures enhanced tau spread after tau seeding, exacerbate cognitive deficits, and that AD transgenic mice are more susceptible to seizures. Thus, targeting seizure activity through pharmacological methods may slow cognitive decline and pathological progression in AD.

**Disclosures: K. Hoag:** None. **A. Barbour:** None. **X. Li:** None. **S. Zebrowitz:** None. **C. Hassman:** None. **V.M.Y. Lee:** None. **D.M. Talos:** None. **F.E. Jensen:** None.

**Poster**

**PSTR013. Tau: Aggregation and Phosphorylation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR013.05/E20

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

**Support:** NIH Grant R01AG077692
NIH Grant T32AG000255
Alzheimer's Association Grant AARF-22-972333
NIH Grant R01NS101156

**Title:** Seizures may exacerbate tau spread through dysregulation of synaptic proteins in Alzheimer's disease patients and 5XFAD mice

**Authors: *A. BARBOUR**[1], X. LI[1], K. HOAG[1], S. ZEBROWITZ[1], E. SHRAYER[1], V. M. Y. LEE[1], D. M. TALOS[1], F. E. JENSEN[2];
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**Abstract:** The spread of tau along neuronal connections is central to AD progression and pathological tau may be transmitted by neuronal activity. Tau has been shown to interact with the presynaptic vesicle protein, Synaptogyrin-3 (SYNGR3), and, thus, may facilitate the trans-synaptic spread of tau. On the post-synapse, data indicate that tau internalization can be mediated by interactions with lipoprotein related-related protein 1 (LRP1) and may be enhanced by loss of Bridging Integrator 1 (BIN1). Up to 64% of AD patients display epileptiform activity and we have previously shown that seizures increase phosphorylated tau in the temporal cortex of AD patients and worsen cognitive outcomes. Thus, we hypothesized that seizures may exacerbate the spread of pathological tau in AD through dysregulation of synaptic proteins. To examine seizure effects on tau spread, we quantified postmortem tau pathology scores from 18 brain regions in AD patients with a known seizure history (AD+Sz) and those without (AD-Sz). To determine whether seizures may alter synaptic machinery to facilitate tau spread, we performed western blot for SYNGR3, BIN1, and LRP1 in. In parallel, we used the five times familial AD (5XFAD) mouse model. To induce tau spread in 5XFAD and WT littermates, we used an establish tau seeding model, involving unilateral injection of AD brain-derived tau lysate (AD-tau) into the hippocampus and overlying cortex (1 µg/site) at 3 months of age. Mice then underwent a pentylenetetrazol (PTZ) kindling protocol and brains were harvested for western blot 3 months post AD-tau seeding. We found that AD+Sz show worsened tau pathology across several cortical regions, including the middle frontal gyrus ($p<0.05$), the angular gyrus ($p<0.01$), and the cingulate gyrus ($p<0.05$), without change in subcortical regions (n=11 (AD+Sz); 130 (AD-Sz)). Similarly, western blot revealed significantly increased phosphorylated tau (AT8) in the frontal cortex contralateral to tau injection in 5XFAD subjected to PTZ-induced seizures compared to control 5XFAD mice ($p<0.05$; n=5-9). We also found that AD+Sz showed increased SYNGR3/Synaptophysin ($p<0.05$; n=11-19) and decreased BIN1 ($p<0.05$; n=8-9), but no change in LRP1 compared to AD-Sz in the temporal cortex. Similarly, kindling decreased BIN1 across

WT and 5XFAD mice in the hippocampus ipsilateral to tau injection ($p<0.05$; n=9-12), with no change in SYNGR3 and LRP1. Overall, these results indicate that seizures may dysregulate synaptic proteins to facilitate the spread of tau and therefore targeting seizure activity may slow AD progression.

**Disclosures: A. Barbour:** None. **X. Li:** None. **K. Hoag:** None. **S. Zebrowitz:** None. **E. Shrayer:** None. **V.M.Y. Lee:** None. **D.M. Talos:** None. **F.E. Jensen:** None.

**Poster**

**PSTR013. Tau: Aggregation and Phosphorylation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR013.06/E21

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

**Title:** Evaluation of sex differences in the Tau P301S mouse model

**Authors: *K. L. MCCURN**[1], A. M. OSSE[3], A. A. ORTIZ[2], B. BALSAMO[2], J. W. KINNEY[2]; [1]Dept. of Brain Hlth., [2]Univ. of Nevada, Las Vegas, Las Vegas, NV; [3]Univ. of Nevada Las Vegas, Las Vegas, NV

**Abstract:** Alzheimer's disease (AD) is a neurodegenerative disease that is characterized by diminished cognitive functioning that leads to memory loss. Pathologically, AD is characterized by the presence of amyloid beta (Aβ) plaques, neurofibrillary tangles (NFTs), and chronic neuroinflammation. NFTs are composed of hyperphosphorylated tau proteins (pTau) that are found in the cell bodies of neurons. Tau proteins are responsible for the microtubule assembly and maintenance of their structural durability. Phosphorylation of tau protein allows trafficking of cargos throughout the cells, however, in AD brains, hyperphosphorylation leads to the inability of tau to attach to the microtubules, resulting in the collapse of these structures, resulting in the accretion of NFTs. Previous studies have demonstrated that female patients with AD have significantly higher levels of tau detected than males. With two-thirds of AD patients being women, there is a need to further research how male and female brains differ in terms of tau pathologies, considering historically most research has been centered around the male brain. Investigation into tau pathologies and how they differ between sexes is critical to deepening our understanding of AD. To assess this, we utilized the well-established Tau P301S mouse to investigate differences in tau pathology between male and female mice through cellular and molecular techniques, including Western blot. These techniques were used to evaluate several protein targets that have been demonstrated to differ in other animal models of AD. Investigation of these targets through implementation of our male and female tau models provided a better understanding of the prevalence of tau pathologies amongst the sexes. This study demonstrates how tau and tau-related proteins compare between males and females, providing insight into the prevalence difference between sexes in AD.

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**Poster**

**PSTR013. Tau: Aggregation and Phosphorylation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR013.07/E22

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

**Title:** Evaluating a mouse model with loss of $GABA_B$receptors crossed with a tau model

**Authors: *A. M. L. OSSE**, A. A. ORTIZ, B. BALSAMO, J. W. KINNEY;
Brain Hlth., Univ. of Nevada Las Vegas, Las Vegas, NV

**Abstract:** Alzheimer's Disease (AD) is a neurodegenerative disease that is clinically described as progressive learning and memory deficiencies. Pathologically, AD is characterized by the presence of three core features, beta-amyloid plaques (Aβ), neurofibrillary tangles (NFT) composed of hyperphosphorylated tau protein, and chronic neuroinflammation. The activation of the immune response through glia cells is associated with neuroinflammation and has been shown to promote and exacerbate both Aβ and NFT pathologies. Alterations in gamma amino butyric acid (GABA), the principle inhibitory neurotransmitter in brain, shown to be involved in several processes, have been demonstrated in AD patients. In addition, GABAergic signaling markers, including the metabotropic receptor $GABA_B$, have also been shown to be altered in an AD animal model (Salazar 2021). $GABA_B$ receptors are expressed on glia and demonstrate anti-inflammatory properties. Loss of this receptor could play an important role in exacerbating the disease.To investigate this, our lab developed a novel mouse model with the loss of the $GABA_B$ receptor restricted to glia (GAB/CX3ert). In our recent publication, we reported transcript and network activity changes in the GAB/CX3ert mice, that were consistent with the APP/PS1 amyloid model, indicating an overlap in the pathways altered (Osse 2023). Additionally, when we crossed the GAB/CX3ert mice with the APP/PS1 mice (GAB/CX3ert x APP/PS1), there were significant increases in Aβ-40 and Aβ-42 (Osse 2023). To determine if the alterations in the GAB/CX3ert mice and the exacerbation of Aβ is specific to amyloid pathology, we crossed the GAB/CX3ert mice with a well-established tau model, Tau P301S. The GAB/CX3ert x Tau P301S mice were evaluated by several cellular and molecular techniques, including immunohistochemistry, qRT-PCR, and Western blot. Males and females were included in the study to assess both sexes for alterations.

**Disclosures:** **A.M.L. Osse:** None. **A.A. Ortiz:** None. **B. Balsamo:** None. **J.W. Kinney:** None.

**Poster**

**PSTR013. Tau: Aggregation and Phosphorylation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR013.08/E23

**Topic:**

**Support:** AG042178
NS205473
AG060767
AG069333
AG066347
AG079264
AG063162
AG071560

**Title:** Protective effects of Citalopram against phosphorylated Tau induced neurotoxicities in the dorsal raphe nucleus

**Authors: *N. SAWANT**[1], S. KSHIRSAGAR[1], L. BUNQUIN[1], P. REDDY[1,2], N. ROHR[2], R. ALVIR[2], A. BUSHRA[2], A. REDDY[2];
[1]Intrnl. Med., Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX; [2]Nutritional Sci., Texas Tech. Univ., Lubbock, TX

**Abstract: Background:** Depression is among the most common neuropsychiatric comorbidities in many Tauopathies, including Alzheimer's disease (AD). Apart from its anti-depressive and anxiolytic effects, selective serotonin reuptake inhibitor (SSRI) treatment also offers intracellular modifications that may help to improve neurogenesis, amyloid burden, Tau pathology, and neuroinflammation. Despite its multifaceted impact in the brain, the exact physiological and molecular mechanism by which SSRIs such as Citalopram improve neurogenesis and synaptogenesis in dementia is poorly understood. **Purpose:** In the present study, we explored phosphorylated Tau (pTau) related cellular changes in AD, as well as protective effects of Citalopram on the dorsal raphe nucleus (DRN), which is the largest serotonergic nucleus in the brain. **Methods:** We investigated pTau, TPH2, SERT, 5HTR1a, Synaptophysin and PSD95, mRNA and protein levels by RT-qPCR, immunoblotting and immunofluorescence analyses in Citalopram treated and untreated Tau mouse models as well as in serotonergic RN46A-B14 neurons, transfected with wild-type and mutant Tau cDNA. Additionally, we also conducted cell survival and mitochondrial bioenergetics (Seahorse) analyses on the RN46A-B14 neurons, and behavioral studies and Golgi-cox staining on the mice. **Results:** Citalopram treatment reduced pTau, SERT, and 5HTR1a levels, while up-regulating Synaptophysin and PSD95 levels in both mouse and cell models of Tau. These findings were endorsed by the increased dendritic spine density and improved cognitive behavior of the treated mice compared to that of the untreated ones. Further, Citalopram also increased cell survival and maximal oxygen consumption rate in RN46A-B14 neurons that express p-Tau. Statistical significance was determined, using one-way ANOVA. **Conclusions:** Taken together these findings suggest that pTau could be playing a critical role in the serotonergic pathway and therefore, Citalopram could not only be a promising therapeutic drug for depression, but also to delay the disease progression in AD patients.

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**Poster**

**PSTR013. Tau: Aggregation and Phosphorylation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR013.09/E24

**Topic:** C.02. Alzheimer"s Disease and Other Dementias

**Support:** R01AG042178
R01AG47812
R01NS105473
AG060767
AG069333
AG066347
AG079264

**Title:** Association between Brain Scans and MoCA Scores in Individuals with Healthy and Impaired Cognition in Rural West Texas.

**Authors: *T. BASU**[1], U. SEHAR[1], J. CULBERSON[2], K. MALHOTRA[4], E. ORLOV[1], H. MORTON[1], C. BOSE[1], L. GITTNER[3], H. KHAN[3], H. REDDY[1];
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**Abstract:** **Background and Purpose:** Alzheimer's disease (AD) in an incurable disease that affects millions of elderly across the globe. Currently, mild cognitive impairment (MCI), a precursor to AD, is diagnosed using the Montreal Cognitive Assessment (MoCA) test in clinical settings. Brain atrophy as measured by structural magnetic resonance imaging (MRI) scans is a potential marker of MCI/AD, yet to be established. In the rural community of West Texas, there is an observed heterogeneity among individuals aged 60-90 years, with some maintaining their cognitive abilities while others experiencing cognitive decline. The purpose of this study is to investigate how MRI images can provide insights into cognitive abilities as assessed by the MoCA test within this population. **Methods:** This ongoing, longitudinal prospective cohort study hopes to recruit 1000 cognitively healthy and 500 MCI/AD patients to understand the associations between structural brain atrophy and cognitive health. This is done by conducting MoCA tests and MRI scans. Overall MoCA scores, MoCA sub scores and structural brain atrophy is analyzed to identify any links, patterns, and/or irregularities in brain structure or function that may indicate cognitive decline. **Results and Discussion:** Currently our study is in year one and has recruited 25 healthy and 5 MCI/AD patients. Our preliminary data strongly indicates that poor overall scores on the MoCA and MoCA memory subscores, are directly associated with the incidence of brain atrophy as seen through MRIs. **Conclusion:** Based on our current data, it is evident that there is an association between cognitive status as determined by

the MoCA test and brain atrophy. This investigation has the potential to advance our understanding of the neurological changes associated with cognitive function and improve early detection and monitoring of conditions like MCI/AD and other types of dementia.

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**Poster**

**PSTR013. Tau: Aggregation and Phosphorylation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR013.10/E25

**Topic:** C.02. Alzheimer"s Disease and Other Dementias

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NIH grant R01AG47812
NIH grant R01NS105473
NIH grant AG060767
NIH grant AG069333
NIH grant AG066347
NIH grant AG079264

**Title:** Unraveling the Impact of Lifestyle and Biological Factors on Cognitively Healthy Superior Agers in Rural West Texas

**Authors: *U. SEHAR**[1], T. BASU[2], J. CULBERSON[3], K. MALHOTRA[4], E. ORLOV[2], H. MORTON[2], C. BOSE[2], L. GITTNER[5], H. KHAN[6], H. REDDY[2];
[1]Texas Tech. Univ. Healthy Sci. Ctr., Lubbock, TX; [2]Dept. of Intrnl. Med., [3]Dept. of Family Med., [4]Grace Clinic, Covenant Hlth. Syst., [5]Dept of Publ. Hlth., Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX; [6]Texas Tech. Univ. Hlth. Sci. Ctr., Dept of Public Health, TX

**Abstract: Background and Purpose:** Alzheimer's disease (AD) is a worldwide pandemic that affects the elderly, causing devastating consequences without a cure. Dementia's contributing factors include lifestyle choices, genetics, epigenetics, and socio-economic circumstances. In rural West Texas, cognitive health varies among those aged 60-90, some experience no impairments, and age gracefully while others face progressive decline with age. The underlying factors for these differences are not clearly understood. Our study examines the lifestyle and biological factors associated with successful cognitive aging in this region. **Methods:** Our longitudinal cohort study investigates factors impacting cognitive status in individuals aged 60-90. We aim to enroll 4000 cognitively healthy participants and 500 with MCI and AD/ADRD. The objective is to identify factors that contribute to delayed aging by exploring genetics, epigenetics, ethnicity, biology, culture, and lifestyle. To gather relevant data, we will assess participants' cognitive abilities using the Montreal Cognitive Assessment (MoCA), record

anthropometric measurements, analyze blood profiles, and administer socio-demographic and behavioral questionnaires. **Results and Discussion:** At present, our study is in its first year and has successfully recruited 25 cognitively healthy individuals and 5 patients with AD. Through the assessment of bloodwork and questionnaires, we have observed that the cognitively healthy population exhibits higher levels of physical and mental well-being. Additionally, we have identified a correlation between a healthy lifestyle, including factors such as sleep, diet, and exercise, and successful aging in the cognitively healthy group. **Conclusion:** Our current data indicate a clear association between scores on the MoCA test, blood biomarkers, and psychosocial parameters. The findings of the study are highlighting the pivotal significance of sufficient nutrition and lifestyle factors in preserving cognitive well-being and mitigating the risk of cognitive decline and its progression to dementia. These findings are significant and contribute to our understanding of healthy aging in the rural West Texas population. The outcomes of our study are anticipated to provide fresh and valuable insights into the factors influencing successful aging in this specific region.

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**Poster**

**PSTR013. Tau: Aggregation and Phosphorylation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR013.11/E26

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

**Support:** R01AG042178
R01AG47812
R01NS105473
AG060767
AG069333
AG066347
AG079264

**Title:** Rlip reduction induces oxidative stress and mitochondrial dysfunction in mutant tau immortalized hippocampal neurons: Mechanistic insights

**Authors: *P. REDDY**[1], S. KSHIRSAGAR[1], C. BOSE[1], J. PRADEEPKIRAN[1], A. HINDLE[1], S. SINGH[1,2], A. REDDY[2], J. BAIG[1];
[1]Intrnl. Med., Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX; [2]Nutritional Sci., Texas Tech. Univ., Lubbock, TX

**Abstract: Abstract:** RalBP1 (Rlip) is a stress-activated protein that believed to play a large role in aging and neurodegenerative diseases such as Alzheimer’s disease (AD) and other

tauopathies. The purpose of our study is to understand the role of Rlip in mutant Tau-expressed immortalized hippocampal HT22 cells. **Methods:** In the current study, we used mutant Tau (mTau) expressed HT22 neurons and HT22 cells transfected with Rlip-cDNA and/or RNA silenced, and studied cell survival, mitochondrial respiration, mitochondrial function, immunoblotting & immunofluorescence analysis of synaptic and mitophagy proteins and colocalization of Rlip and mTau proteins. We found Rlip protein levels were reduced in mTau-HT22 cells, Rlip silenced HT22 cells and mTau + Rlip RNA silenced HT22 cells; on the other hand, increased Rlip levels were observed in Rlip cDNA transfected HT22 cells. **Results:** We found cell survival was decreased in mTau-HT22 cells and RNA-silenced HT22 cells. However, cell survival was increased in Rlip-overexpressed mTau-HT22 cells. Significantly reduced oxygen consumption rate (OCR) was found in mTau-HT22 cells and in RNA-silenced Rlip-HT22 cells and even greater reduction in mTau-HT22+Rlip RNA-silenced HT22 cells. Significantly increased OCR was found in Rlip-overexpressed HT22 cells and in all groups of cells that overexpress Rlip cDNA. Mitochondrial function was defective in mTau-HT22 cells, RNA silenced Rlip in HT22 cells and further defective in mTau-HT22+Rlip RNA-silenced HT22 cells; however, it was rescued in Rlip overexpressed in all groups of HT22 cells. Synaptic and mitophagy proteins were decreased in mTau-HT22 cells, further reductions were found in RNA-silenced mTau-HT22 cells. However, these were increased in mTau+Rlip overexpressed HT22 cells. An increased number of mitochondria and decreased mitochondrial length were found in mTau-HT22 cells. These were rescued in Rlip overexpressed mTau-HT22 cells. **Conclusions**: These observations strongly suggest that Rlip deficiency causes oxidative stress/mitochondrial dysfunction and Rlip overexpression reverses these defects. Overall, our findings revealed that Rlip is a promising new target for aging, AD and other tauopathies/neurological diseases that showed the relevance of oxidative stress and mitochondrial dysfunction in the disease process.

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**Poster**

**PSTR013. Tau: Aggregation and Phosphorylation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR013.12/E27

**Topic:** C.02. Alzheimer"s Disease and Other Dementias

**Support:** RF1AG079264

**Title:** Increased Lifespan of MicroRNA-455-3p Mouse Models of Alzheimer's Disease: Possible Protective Role of Mitophagy

**Authors: *J. BAIG**[1], H. P. REDDY[2];
[1]3601 4th street, Lubbock, TX; [2]Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

**Abstract:** MicroRNA (miRs) are small, single-stranded, non-coding RNA molecules reported to be involved in RNA silencing and post-transcriptional regulation of gene expression in cells. Multiple miRs have been studied in our lab, but overexpressed miR-455-3p in mice (miR-455-3p Tg mice) was observed to increase cognitive and memory functions and increase lifespan five months longer than the wild-type (WT) mice, whereas miR-455-3p knockout (KO) mice lived four months shorter than WT mice, but the exact mechanism of increased lifespan in miR-455-3p Tg mice is unknown. In Alzheimer's disease (AD), defective mitophagy, selective removal of dead/damaged mitochondria, was observed in AD cells, AD mice, and AD brains. We hypothesize that mitophagy may play a key role in the enhanced lifespan of miR-455-3p Tg mice compared to its WT counterparts. Messenger RNA and protein levels of 17 genes that are associated with mitophagy, were studied using the cortical brain tissues of miR-455-3p Tg, miR 455-3p KO, and WT mice at two timepoints: 2 months and 12 months. The overall, early preliminary data revealed mitophagy genes and proteins had an increase in expression in MiR-455-3p Tg mice and a decrease in expression in MiR-455-3p KO mice compared to their WT counterparts, indicating an increase in mitophagy in the cells in MiR-455-3p Tg mice compared to WT mice. These results suggest that enhancement of mitophagy in MiR-455-3p Tg mice compared to their WT counterparts may be contributing to the increased lifespan in mice, and thus may have a protective role in AD and other age-related diseases.

**Disclosures: J. Baig:** None. **H.P. Reddy:** None.

**Poster**

**PSTR013. Tau: Aggregation and Phosphorylation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR013.13/E28

**Topic:** C.02. Alzheimer"s Disease and Other Dementias

**Support:** R01AG042178,
R01AG47812,
R01NS105473,
AG060767

**Title:** The Role of RLIP76 in Oxidative Stress and Mitochondrial Dysfunction: Evidence Based on Autopsy Brain from Alzheimer's Disease Patients

**Authors: *C. BOSE**, S. KHIRSAGAR, S. P. SINGH, S. KUMAR, M. VIJAYAN, P. REDDY; IM, Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

**Abstract:** The role of RLIP76 (AKA Rlip) in Alzheimer's and other neurodegenerative diseases is not known completely. Several converging lines of evidence from our group and others support a potential role of Rlip in neurodegenerative disorders, including AD. Because oxidative stress appears to play an important role in the pathophysiology of AD and progression of the disease, the purpose of the present study is to determine the role of Rlip in the brains of AD

patients and control subjects. To achieve our goals, we used frozen tissues, and formalin fixed paraffin-embedded postmortem brains from AD patients with different Braak stages and age matched controls subjects. Our immunohistology and western blot results demonstrates that expression of Rlip protein gradually and significantly decreased ($p<0.0001$) with AD progression and being lowest in Braak stage IV-V. Rlip was colocalized with Amyloid beta (Aβ) and phosphorylated tau (p-Tau) as observed by IHC staining and co-immunoprecipitation studies. Lipid peroxidation, 4-HNE generation and H2O2 production were significantly higher ($p<0.004$ and 0.0001 respectively) in AD patients compared to controls accompanied by lower ATP production in AD ($p<0.0009$). Oxidative DNA damage was measured by 8-Hydroxyguanosine (8-OHdG), in tissues lysates by ELISA and COMET assay. AD 8-OHdG levels were significantly higher ($p<0.0001$) compared to controls. COMET assay was performed in brain cells, isolated from frozen postmortem brain samples. The control samples showed minimal DNA in comets representing few DNA strand breaks (<20%), (score-0-1). However, AD group showed an average of 50% to 65% of DNA in comet tails (score-4-5) indicating numerous DNA strand breaks. Difference between two groups was significant ($p<0.001$), as analyzed by Open Comet by ImageJ. Elevated DNA damage was further examined by western blot analysis for phosphorylated histone variant H2AX (γH2AX), Induction of γH2AX is very significant ($p<0.0001$) and confirmed the double DNA strand breaks and damage. Overall, our results indicate an important role for Rlip in maintaining neuronal cell health and homeostasis by suppressing cellular oxidative stress and DNA damage. Based on our findings, we cautiously conclude that Rlip is therapeutic target for ALZHEIMER's DISEASE.

**Disclosures: C. bose:** None. **S. Khirsagar:** None. **S.P. Singh:** None. **S. Kumar:** None. **M. Vijayan:** None. **P. Reddy:** None.

**Poster**

**PSTR013. Tau: Aggregation and Phosphorylation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR013.14/E29

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

**Support:** NIH U24DK115255
NIH R01DK130913
the Sinai Medical Staff Foundation
the Robert E. Nederlander Sr. Program for Alzheimer's Research
the Andrea and Lawrence A. Wolfe Brain Health Initiative Fund
the A. Alfred Taubman Medical Research Institute
the NeuroNetwork for Emerging Therapies

**Title:** Palmitate modulates neuroglial interaction through the extracellular vesicles: possible link between metabolic syndrome and Alzheimer's disease.

**Authors: *B. KIM**[1,2], Y.-T. KANG[3], F. E. MENDELSON[2], J. M. HAYES[2], M. G. SAVELIFF[2], S. NAGRATH[3], E. L. FELDMAN[4];
[2]Neurol., [3]Chem. Engin., [1]Univ. of Michigan, Ann Arbor, MI; [4]Neurolgy, Univ. of Michigan, Ann Arbor, Ann Arbor, MI

**Abstract:** The metabolic syndrome (MetS) and Alzheimer's disease share several pathological features, including insulin resistance, abnormal protein processing, mitochondrial dysfunction, and elevated inflammation and oxidative stress. The MetS constitutes elevated fasting glucose, obesity, dyslipidemia, and hypertension and increases the risk of developing Alzheimer's disease, but the precise mechanism remains elusive. Insulin resistance, which develops from a diet rich in sugars and saturated fatty acids, such as palmitate, is shared by the MetS and Alzheimer's disease. Extracellular vesicles (EVs) are also a point of convergence, with altered dynamics in both the MetS and Alzheimer's disease. However, the role of palmitate-induced insulin resistance in the brain and its potential link through exosomes to Alzheimer's disease is unknown. We demonstrate that palmitate induces insulin resistance and amyloid precursor protein (APP) phosphorylation in primary rat embryonic cortical neurons and human cortical stem cells. Palmitate also triggers insulin resistance in oligodendrocytes, the supportive glia of the brain. Palmitate enhances APP secretion from cortical neurons via EVs, which induces tau phosphorylation when treated to naïve neurons. Additionally, EVs from palmitate-treated oligodendrocytes enhance insulin resistance in recipient neurons. Overall, our findings suggest a novel theory underlying the increased risk of Alzheimer's disease in MetS mediated by EVs, which spread Alzheimer's pathology and insulin resistance. The authors received funding support from the NIH (U24DK115255, R01DK130913). The authors would like to thank the Sinai Medical Staff Foundation, the Robert E. Nederlander Sr. Program for Alzheimer's Research, the Andrea and Lawrence A. Wolfe Brain Health Initiative Fund, the A. Alfred Taubman Medical Research Institute, and the NeuroNetwork for Emerging Therapies. The authors appreciate the support from the Michigan Diabetes Research Center for the confocal imaging.

**Disclosures: B. Kim:** None. **Y. Kang:** None. **F.E. Mendelson:** None. **J.M. Hayes:** None. **M.G. Saveliff:** None. **S. Nagrath:** None. **E.L. Feldman:** None.

**Poster**

**PSTR013. Tau: Aggregation and Phosphorylation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR013.15/E30

**Topic:** C.09.Stroke

**Support:** NIH RO1NS119395
NIH RO1MH125429
American Heart Association

**Title:** Early phosphorylation of tau revealed during the hyperacute phase of stroke in non-human primates

**Authors: *N. STANIS**[1], E. PERES VERRATTI[2], J. ZHOU[2], K. KHATEEB[2], H. JAHANIAN[1], A. YAZDAN-SHAHMORAD[3];
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**Abstract:** Until recently, Alzheimer's disease (AD) has been widely accepted as a neurodegenerative disorder; however, the coexistence of cerebrovascular changes with cognitive decline implies this may be more in line with a vascular disorder. Two biomarkers, Neurofibrillary tangles (NFTs) and amyloid beta (AB), signal the presence of AD and have been shown to appear following ischemic stroke as well. In rodents, it has been shown that amyloid precursor protein accumulates 3 days after stroke while its cleaved product, amyloid beta, accumulates 7 days after stroke. Furthermore, tau hyperphosphorylation, which leads to the formation of NFTs, has been shown to manifest at a much earlier time point of 24 hours.
To further investigate tau phosphorylation after stroke we employed a photothrombotic ischemic stroke model in the motor cortex of 6 non-human primates (NHPs). Furthermore, we administered an electrical simulation protocol to the peri-infarct area of 2 of these animals to potentially improve clearance of this pathological tau isoform in a clinically relevant animal model. Stimulation (60 mA, 5 biphasic pulses per burst at 1 kHz, 450 ms pulse width, 50 ms interphase interval, 5 Hz burst frequency) occurred in six ten-minute blocks interspaced with 2-minute resting blocks. Brains were harvested 3 hours later during the hyperacute phase of stroke, and immunohistochemistry staining was performed to identify specific phosphorylated sites of tau (Ser422, Ser202, Thr205).
For the first time with this stroke model, we have identified phosphorylation of the Ser422 site in the peri-infarct area at a time point much earlier than previously reported. This marker colocalized to both the somas and axons of neural and non-neural cell populations. On the stimulated side of the lesion we saw a reduction in the number of cells with tau-Ser422 phosphorylation. As a control, we performed staining on the contralesional hemisphere, and as a result, found no positive staining.
It is well documented that AD biomarkers appear after stroke, yet here we show the earliest time point that has yet to be investigated with a clinically significant animal model. During the hyperacute phase of stroke, the necrotic core is still expanding into the penumbra, leaving a peri-infarct area rich with information about how neurodegeneration may be occurring through vascular disorder. Our preliminary results indicating abnormal tau phosphorylation in this region demonstrate spatial dependence of tau disruption which is an observation highly relevant to the emergence of AD. Additionally, electrical stimulation has demonstrated a neuroprotective effect by mitigating the pathological tau phosphorylation.

**Disclosures:** **N. Stanis:** None. **E. Peres Verratti:** None. **J. Zhou:** None. **K. Khateeb:** None. **H. Jahanian:** None. **A. Yazdan-Shahmorad:** None.

**Poster**

**PSTR013. Tau: Aggregation and Phosphorylation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR013.16/E31

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

**Support:** CZI Grant 601413.1
R01 SFP_300234.1

**Title:** Real-time monitoring of tau aggregation in a human in vitro model of tau pathology

**Authors: *S. VAFAIE-PARTIN**;
Vanderbilt Univ., Nashville, TN

**Abstract:** Title: Real-time monitoring of tau aggregation in a human *in vitro* model of tau pathology
Authors: Sidney Vafaie-Partin[1], Lauren Drake[2], Brian O'Grady[3], Ethan Lippmann[2,3]; [1]Vanderbilt University Department of Biological Sciences, [2]Vanderbilt University Department of Biomedical Engineering, [3]Vanderbilt University Department of Chemical Engineering Disclosures: Sidney Vafaie-Partin (none), Lauren Drake (none), Brian O'Grady (none), Ethan Lippmann (none)
Abstract:Tau protein and the insoluble aggregates it forms have been implicated in over twenty neurodegenerative diseases known as tauopathies, including Alzheimer's disease (AD) and frontotemporal dementia (FTD). Pathogenic tau aggregates exhibit a diverse array of post-translational modifications and structures. Due to this variation, there is considerable heterogeneity among tauopathies. This poses a considerable challenge for the study of these diseases and the development of widely applicable models, while also highlighting the need for a patient-specific precision-medicine approach to tauopathy treatment. To that end, we have developed a model system for the *in vitro* study of tauopathies using human induced pluripotent stem cell (iPSC)-derived excitatory neurons to mimic the environment of the frontal cortex. Paired with our fluorescence resonance energy transfer (FRET) biosensor for aggregated tau, this model provides a promising tool for the study of tauopathies. To build the model, dual chamber microdevices were seeded with stem cell-derived neurons expressing the biosensor. One chamber contained neurons exposed to aggregated tau seeds derived from cell lysates or solubilized postmortem human brain tissue. The brain tissue was obtained from AD, FTD, and control patients. The other chamber contained neurons not exposed to tau seeds. We demonstrated the biosensor's ability to fluorescently report tau propagation from the human brain and cell lysates and quantified the propagation of aggregated tau within the microdevice. The model's capacity for real-time imaging of spreading tau pathology, which is impossible in *in vivo* models, provides a promising template for further studies on the mechanisms of tau spread. Furthermore, we aim to improve the system by adding iPSC-derived astrocytes and microglia to better mimic the *in vivo* environment. This immunorepresentative system will have greater biological relevance and will allow for us to further understand the interaction of these cell types with tau aggregates and afflicted neurons.
*Figure : Experimental Summary*

**Disclosures: S. Vafaie-Partin:** None.

**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.01/E32

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

**Support:** R01 DC014296
R21 DC019567
R21 AG073744

**Title:** Measuring Sentence Information via Surprisal: Clinical and Theoretical Implications in Nonfluent Aphasia

**Authors: *N. REZAII**[1], J. MICHAELOV[3], S. E. JOSEPHY HERNÁNDEZ[4], B. REN[2], M. QUIMBY[1], D. HOCHBERG[1], B. C. DICKERSON[5];
[1]Harvard Med. Sch., Boston, MA; [2]Harvard Med. Sch., Belmont, MA; [3]UCSD, San Diego, CA; [4]McGill Univ., Montreal, QC, Canada; [5]Neurol., Massachusetts Gen. Hosp. Dept. of Neurol., Charlestown, MA

**Abstract:** Nonfluent aphasia is characterized by simplified sentence structures and word-level abnormalities, including reduced use of verbs and function words. The predominant understanding of the disease mechanism is that a core deficit in syntax processing causes both structural and word-level abnormalities. Under this agrammatic account, it remains unclear why nonfluent patients choose semantically richer verbs and may have a spared comprehension of verbs and function words. While often dismissed by the agrammatic account, these unexplained features may point to a distinct language process critical for communication in nonfluent aphasia. Here, we hypothesize that the word-level features of nonfluency constitute a distinct compensatory process that augments the information content of sentences to the level of healthy speakers. We use a computational approach based on Language Models (LMs) to measure sentence information through surprisal, a metric calculated by the average probability of occurrence of words in a sentence, given their preceding context. We apply this method to the language of patients with nonfluent primary progressive aphasia (nfvPPA) (n=36) and healthy controls (n=133) as they partake in a picture description task. We found that nfvPPA patients produced sentences with the same sentence surprisal as healthy controls using richer words in structurally simpler sentences. Furthermore, higher surprisal in nfvPPA sentences correlated with the canonical features of agrammatism: a lower function-to-all-word ratio, a lower verb-to-noun ratio, a higher heavy-to-all-verb ratio, and a higher ratio of verbs in gerund forms. Using surprisal enables testing an alternative account of the disease that regards the word-level features of nonfluency as adaptive, rather than defective, symptoms, a finding that would call for revisions in the therapeutic approach to nonfluent language production.

**Disclosures: N. Rezaii:** None. **J. Michaelov:** None. **S.E. Josephy Hernández:** None. **B. Ren:** None. **M. Quimby:** None. **D. Hochberg:** None. **B.C. Dickerson:** None.

**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.02/E33

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

**Support:** NIH Grant 1RF1 AG057181-01

**Title:** Co-occurrence of argyrophilic grain disease pathology is associated with lower brain Aβ and p-tau accumulation in Alzheimer's disease

**Authors: *A.-C. RAULIN**, S. V. DOSS, T. C. IKEZU, Y. A. MARTENS, Z. H. LI, C.-C. LIU, H. SEKIYA, L. KUCHENBECKER, E. CRAVER, M. G. HECKMAN, M. E. MURRAY, D. W. DICKSON, G. BU, T. KANEKIYO;
Mayo Clin., Jacksonville, FL

**Abstract: Background:** Alzheimer's disease (AD) is defined by the deposition of amyloid-β beta (Aβ) plaques and neurofibrillary tangles (NFT) composed of phospho-tau (p-tau). However, coexisting pathology in AD is commonly observed, including age-related tauopathies such as 4R-tau predominant argyrophilic grain disease (AGD). The impact of AGD on Aβ pathology was previously reported at the neuropathologic level, but how AGD pathology associates biochemically with AD is not fully understood yet.
**Methods:** We investigated the temporal cortex from a large, neuropathologically-defined cohort of AD and control who had available *APOE* genotypes (n=365). *APOE* genotype groups included: *APOE2* (n=46, including *APOE2/2* and *APOE2/3*), *APOE3* (n=162, consisting of *APOE3/3),* and *APOE4* (n=157, including *APOE3/4* and *APOE4/4*). Biochemical amounts of major AD-related molecules were measured by ELISA and included: $A\beta_{40}$, $A\beta_{42}$, total tau , p-tau181, and apolipoprotein E (apoE).
**Results:** We found that cognitive impairment in dementia cases is dependent on neuropathology. More specifically, Mini-Mental State Examination (MMSE) scores in the cohort were correlated with a neuropathologic diagnosis of AD. Amounts of AD-related molecules in the brain of dementia cases were associated with the presence of tau lesions characteristic of AD (referred to as AD tau), but not with tau lesions consistent with the presence of AGD (referred to as 4R tau). Cognitive decline as shown by MMSE was also linked to the presence of AD tau, but not 4R tau. When assessing AD cases, our biochemical data demonstrated that the presence of 4R tau neuropathologic lesions consistent with an AGD diagnosis was associated with lower $A\beta_{42}$ and p-tau181 levels.
**Conclusions:** These results support the neuropathologic evidence that co-occurrence of AGD with AD is associated with lower Braak stage and Thal phase, with the presence of neuropathologically defined 4R tau lesions associated with lower levels of AD-related molecules in mixed AD cases.

**Disclosures: A. Raulin:** None. **S.V. Doss:** None. **T.C. Ikezu:** None. **Y.A. Martens:** None. **Z.H. Li:** None. **C. Liu:** None. **H. Sekiya:** None. **L. Kuchenbecker:** None. **E. Craver:**

None. **M.G. Heckman:** None. **M.E. Murray:** None. **D.W. Dickson:** None. **G. Bu:** None. **T. Kanekiyo:** None.

**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.03/E34

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

**Support:** NIH P30 AG066507

**Title:** Beyond AD: neuropathological and cognitive outcomes of >80 years of age participants free of AD pathological lesions in a longitudinal community-based cohort

**Authors: J. REDDING-OCHOA**[1], K. CHANG[1], Y. AN[4], A. MOGHEKAR[2], S. M. RESNICK[5], M. ALBERT[6], A. BARRETT[1], T. PYLYUKH[7], *J. TRONCOSO[3]; [1]Pathology, [2]Neurol., [3]Johns Hopkins University, Sch. of Med., Baltimore, MD; [4]NIA, NIH, Baltimore, MD; [5]Natl. Inst. on Aging, Natl. Institues of Hlth., Baltimore, MD; [6]Johns Hopkins Univ., Baltimore, MD; [7]NIH, Bethesda, MD

**Abstract:** The goal of our study is to assess the neuropathology and cognition in older individuals free of Alzheimer's disease (AD) neuropathological changes, the most common cause of dementia in the older population. However, in advanced age there are multiple morbidities other than AD that may have an impact in cognition as demonstrated by clinical; and postmortem studies. Using pooled data from the Johns Hopkins Alzheimer's Disease Center including participants from the Baltimore Longitudinal Study of Aging (BLSA)(n=62) and Clinic cohort(n=15), we examined the neuropathological and cognitive outcomes of 77 participants, ≥ 80 years of age, whose brains were free of neuritic plaques, i.e., CERAD 0 (average age of death: 89; men: 74%). Diffuse Aβ plaques were present in 15 brains (19%). The Braak NFT scores ranged from I to IV (96%) with the presence of neurofibrillary tangles in the medial temporal lobe close to universal (99%). Vascular lesions were present in 46 brains (60%), infarcts in 37 (48 %), hemorrhages in 4 (5%), and mixed lesions in 5 brains (7%). Lewy body pathology (LBP) was noted in 13 brains (17 %). TDP-43 proteinopathy ,i.e., LATE neuropathologic change (NC), was observed in 23% of brains with a cumulative frequency distribution indicating that LATE-NC+ increase drastically around 95 years of age. Cognitive impairment occurred in 51% of the participants, and 39% of them were fully demented at their last clinical evaluation. Logistic regression analyses showed a significant association between LATE-NC+ and cognitive impairment (p=0.03; OR 4.83, 95% CI). The other variables didn't show statistical significance. In conclusion, our study indicates that even in the absence of AD, the older population has a very high risk of cognitive impairment. This information is relevant to public health approaches to aging, dementia, and also the eventual pharmacological prevention of AD.

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**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.04/E35

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

**Support:** Chan Zuckerberg Initiative (Ben Barres Early Career Acceleration Award; grant ID 199150)
Stanford Alzheimer Disease Research Center (NIH/NIA P30 AG066515)

**Title:** Profiling the vulnerable and resistant neuronal subpopulations to Lewy body pathology in diffuse Lewy body disease

**Authors: *J. FORES MARTOS**, K. VALLEJO, S. U. MAHAJANI, D. WAKHLOO, J. PAN, J. E. OBERHAUSER, A. SANKARAESWARAN, M. OTERO-GARCIA, V. DOAN, Y. LIU, I. COBOS;
Stanford Univ., Palo Alto, CA

**Abstract:** Lewy body disease (LBD) represents the second major cause of neurodegenerative dementia after Alzheimer's disease (AD) and is characterized by the intracellular accumulation of α-synuclein-containing aggregates in neurons and neuronal processes (Lewy bodies and neurites). Ninety percent of LBD cases also present AD pathological hallmarks, including neurofibrillary tangles and amyloid-β aggregates. Although regional pathological progression has been well characterized in LBD, with diffuse Lewy body disease (DLBD) presenting abundant cortical Lewy bodies, little is known about the selective vulnerability of specific neuronal subpopulations. We applied single-nucleus RNA-sequencing (snRNA-seq) to human brain tissue from donors with DLBD to characterize the vulnerable and resistant neuronal subtypes in the DLBD brain and the similarities and differences between DLBD and AD. We profiled the prefrontal cortex (BA9) and the amygdala from 16 donors (7 females and 9 males) with a median age of 80 years (53 - 94), of which, 3 had intermediate AD pathology (Braak III-IV) and 13 had high AD pathology (Braak V-VI). We integrated DLBD data with previously generated snRNA-seq data from AD and healthy controls comprising a total of ~630, 000 nuclei. In addition, we studied the neuronal subtype-specific distribution of Lewy bodies by combining RNA in situ hybridization (RNAscope) and phospho-α-synuclein immunohistochemistry. Our data represents a resource for the study of selective cell vulnerability in DLBD.

**Disclosures:** **J. Fores Martos:** None. **K. Vallejo:** None. **S.U. Mahajani:** None. **D. Wakhloo:** None. **J. Pan:** None. **J.E. Oberhauser:** None. **A. Sankaraeswaran:** None. **M. Otero-Garcia:** None. **V. Doan:** None. **Y. Liu:** None. **I. Cobos:** None.

**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.05/E36

**Topic:** C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

**Support:** NINDS Grant NS085770
NIA Grant AG072977

**Title:** Not All Tauopathies are Created Equal

**Authors: *D. L. GARCIA**[1], S. R. DUNLOP[2], Y. NISHIHIRA[3], I. AYALA[3], E. H. BIGIO, 60626[4], R. CASTELLANI[4], T. D. GEFEN[4], M.-M. MESULAM[5], C. GEULA[6];
[1]Mesulam Ctr. for Cognitive Neurol. and Alzheimer's Dis., Northwestern Univ., Evanston, IL; [2]Northwestern Univ. Interdepartmental Neurosci., [4]Mesulam Ctr. for Cognitive Neurol. and Alzheimer's Dis., [3]Northwestern Univ., Chicago, IL; [5]Norrthwestern Univ., Cognitive Neurol. and Alzheimer's Dis. Ctr., Chicago, IL; [6]Mesulam Ctr. for Cognitive Neurol. and Alzheimer's Dis., Northwestern Univ. Med. Sch., Chicago, IL

**Abstract:** Cortical Basal Degeneration (CBD), a subtype of frontotemporal dementia, is a neurodegenerative disease in which pathologic tau accumulation is seen in many brain regions including the frontal lobe, temporal lobe, and subcortical brain structures. This results in progressive loss of verbal communication ability, motor function, and other cognitive deficits. While clinical and behavioral symptoms differentiate CBD from other dementias, the unique underlying pathobiology of CBD is not fully understood. This lack of insight has led to a lack of disease modifying therapeutic treatment options and preventative mechanisms. The basal forebrain cholinergic neurons (BFCNs) are a primary target of tau accumulation in neurofibrillary tangles which lead to cell death in Alzheimer’s Disease (AD). We investigated whether BFCNs are also a primary target for tau protein pathology and degeneration in human postmortem brain tissue from five individuals clinically and pathologically diagnosed with CBD compared to five participants with AD. Immunohistochemistry with antibodies to choline acetyltransferase (ChAT) and low affinity neurotrophin receptor (p75LNTR) were used to visualize BFCNs. The AT8 antibody was used to visualize tau inclusions. Using unbiased stereology to quantify ChAT-, p75LNTR-, and tau-positive BFCN, 53%-81% of ChAT positive BFCNs contained p75LNTR and 44%-72% contained tau protein inclusions. In contrast to what has been reported in AD, we did not observe a negative correlation between the density of ChAT- and AT8-positive BFCN. Participants with similar densities of ChAT-positive BFCN displayed substantially different densities of AT8-positive BFCN. The density of acetylcholinesterase-positive cortical cholinergic axons, which originate from the BFCN, was significantly higher than the density in AD brains. These findings suggest that BFCNs in CBD may be resilient to tau protein induced neurodegeneration, and that the species of pathologic tau may be different in AD when compared with CBD. Our findings also imply that cholinergic based therapies used for treatment of AD and other dementias are likely to be ineffective in

treating CBD and further research is needed to understand the characteristics of tau pathology in CBD and to identify new therapeutic targets.

**Disclosures:** **D.L. Garcia:** None. **S.R. Dunlop:** None. **Y. Nishihira:** None. **I. Ayala:** None. **E.H. Bigio:** None. **R. Castellani:** None. **T.D. Gefen:** None. **M. Mesulam:** None. **C. Geula:** None.

**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.06/Web Only

**Topic:** C.03. Parkinson's Disease

**Support:** Nanostring Technologies

**Title:** Rare neurodegenerative disorders PSP and CBD reveal differential regional neuroinflammatory signatures in the human post mortem brain.

**Authors: *A. J. CURLE**[1], D. B. RAINBOW[1], A. QUAEGEBEUR[1], E. METZGER[2], A. WHITE[2], P. PHAN[2], T. RITTMAN[1], J. B. ROWE[1], J. JONES[1];
[1]Clin. Neurosciences, Univ. of Cambridge, Cambridge, United Kingdom; [2]Nanostring Technologies, Seattle, WA

**Abstract:** The concept that neuroinflammation plays an important role in the pathogenesis of neurodegenerative conditions such as Alzheimer's and Parkinson's disease has gained traction in recent years, culminating in trials of immunotherapies in these conditions. Far less is known about the role of inflammation in progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), two rare "Parkinson-Plus" neurodegenerative tauopathies that currently have no effective treatments. Herein we sought evidence of neuroinflammation in pathogenesis of both PSP and CBD relative to age-matched controls in the prefrontal cortex (PFC) and putamen. We report on gene expression differences in post-mortem brain tissue from 10 PSP, 10 CBD, and 10 age- and sex-matched controls using the nCounter® Neuroinflammation and Glial panels (~1,500 genes). Differential gene expression analysis revealed regional differences between disease tissue and controls and within the disease cohort (PSP vs. CBD). Compared to controls, inflammatory genes were upregulated in CBD PFC, while the putamen was relatively unaffected. In contrast, an inflammatory signature was found in both the putamen and PFC in PSP, suggesting more wide-spread neuroinflammation. Within the PFC, the transcriptional signature seen in CBD was immune related whilst in PSP many of the genes upregulated were related to oligodendrocyte function. In the PFC and putamen, cell type profiling revealed increased microglia, infiltrating macrophages and neutrophils in both CBD and PSP compared to controls. Oligodendrocyte scores were higher in the PSP samples. Pathway analysis of the PFC revealed increased expression of immune and inflammatory pathways in both conditions, with highest enrichment of neutrophil degranulation, IL-6/JAK STAT3 signalling and complement

pathways and downregulation of neuronal genes. When comparing the two diseases, these immune-related pathways were more highly enriched in CBD. In the putamen, immune pathways were enriched in CBD vs controls, but more so in the PSP samples. IFN signalling and response pathways were most enriched in the PSP brains. Together these data show that neuroinflammation plays a role in the pathogenesis of both PSP and CBD, but that inflammation is more localised to the PFC of the CBD and more widespread in PSP. Validation using the GeoMx® Digital Spatial Profiler is underway. This will enable us to better understand differences in disease-specific regional signatures, including covariates such as tau localisation.

**Disclosures: A.J. Curle:** None. **D.B. Rainbow:** None. **A. Quaegebeur:** None. **E. Metzger:** A. Employment/Salary (full or part-time); Nanostring Technologies. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nanostring Technologies. **A. White:** A. Employment/Salary (full or part-time); Nanostring Technologies. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nanostring Technologies. **P. Phan:** A. Employment/Salary (full or part-time); Nanostring Technologies. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nanostring Technologies. **T. Rittman:** None. **J.B. Rowe:** None. **J. Jones:** None.

**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.07/E37

**Topic:** I.06. Computation, Modeling, and Simulation

**Support:** NIH Grant T32GM007057-47

**Title:** Frontal temporal dementia diagnosis using a novel resting-state scalp EEG marker of regional interactions in the brain

**Authors: *L. SANCHEZ**, A. WILLIAMS, A. H. DARAIE, S. V. SARMA;
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**Abstract:** Frontotemporal dementia (FTD) is a rare neurological disorder that affects the prefrontal and anterior temporal cortex, leading to unusual behaviors, emotional problems, communication difficulties, and mobility issues. It represents 12-20% of dementia cases and commonly manifests in individuals aged 45 to 64. For many years, research focused on identifying proteins or substances in the blood or cerebrospinal fluid, to monitor disease progression and assess treatment effectiveness. More recently, scientists are investigating ways to enhance brain imaging techniques and neuropsychological testing. Electroencephalogram (EEG) has emerged as a cost-effective and easily accessible tool for diagnosing and categorizing the severity of dementia. Developing EEG biomarkers to complement neuropsychological tests

for FTD detection is a desirable choice over other neuroimaging devices due to its low cost and accessibility. In this research study, we constructed personalized dynamic "brain" network models (DNMs) based on scalp EEG data from each patient. Using these DNMs, we examined a novel EEG biomarker known as the "sink index," which characterizes how each brain region (node) is influenced by other regions in the brain network. In the model, sources refer to brain regions that exert a significant influence on other regions but are not themselves influenced, while sinks represent influenced regions that do not exert influence on others. Based on this, we hypothesized that brain regions associated with frontotemporal dementia behave as sinks and present higher sink indices compared to healthy brain regions. We tested our hypothesis on a cohort of 23 FTD patients and 29 Healthy Controls (HC) obtained from the open dataset of the Department of Neurology of AHEPA General University Hospital of Thessaloniki. For the analysis, we matched ages for the FTD (67.5 ± 4.5), and HC (68.5 ± 7.2) groups, respectively. Our preliminary results revealed normality test differences for the Sink-Index Distribution of FTD ($p < 0.001$) and HC ($p > 0.1$) suggesting clear pathological state detection. As well, the Sink-Index of the EEG electrodes associated to the frontal-temporal brain regions (Fp1,Fp2,F3,F4,F7,F8,T3,T4) and other regions (O1,T5,O2,T6,Cz,Pz,P3,Fz,P4,C3,C4) display noticeable differences between FTD (1.3389 ± 0.0895 vs. 0.8444 ± 0.0651) and HC (0.8978 ± 0.0453 vs. 0.9116 ± 0.0457). These findings highlight the potential of the sink-index as an EEG biomarker to help in the detection and diagnosis of FTD. A further utility of the sink index is to measure efficacy of treatment by quantifying how much the treated brain returns to more of a healthy state.

**Disclosures: L. Sanchez:** None. **A. Williams:** None. **A.H. Daraie:** None. **S.V. Sarma:** None.

**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.08/E38

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

**Support:** NIH Grant U01MH117023
NIH Grant R01 AG075727
Kilachand Fund 9090013367

**Title:** Imaging Myelin Degradation in Ex Vivo Human Brain Samples: A Comparative Study of Alzheimer's Disease and Chronic Traumatic Encephalopathy

**Authors: *A. NOVOSELTSEVA**[1], J. YANG[1], S. CHANG[1], N. BLANKE[1], G. KURELI[1], P. ANTINEW[1], B. QIU[1], A. CHEN[1], H. WANG[2], I. BIGIO[1], D. BOAS[1], A. MCKEE[1]; [1]Boston Univ., Boston, MA; [2]Athinoula A. Martinos Ctr. for Biomed. Imaging, Mass Gen. Res. Inst., Boston, MA

**Abstract:** Alzheimer's disease (AD) and chronic traumatic encephalopathy (CTE) are incurable neurodegenerative diseases, both of which are characterized by the presence of hyperphosphorylated tau accumulations, which form neurofibrillary tangles. One of the hallmarks of these conditions is progressive axonal degeneration associated with the accumulation of hyperphosphorylated tau. However, the role of myelin degradation, a process that accompanies axonal degeneration, remains relatively unexplored in the pathogenesis of AD and CTE. This study aimed to investigate and visualize myelin degradation in AD and CTE using high-resolution imaging techniques at both microscopic (≤0.5 μm) and mesoscopic (~12 μm) scales. We utilized birefringence microscopy (BRM) and polarization-sensitive optical coherence tomography (PS-OCT) to image and evaluate myelin degradation. We employed a custom-built PS-OCT system for mesoscale imaging, allowing us to quantify tissue optical properties across large volumes at a resolution of ~12 μm. Additionally, we utilized co-registered microscopic imaging with our custom-built BRM system to examine the details of myelin degradation at a higher resolution. Thirteen human brain samples from the dorsolateral prefrontal cortex were imaged and analyzed, including three age-matched normal controls (NC), five late-stage AD cases, and five late-stage CTE cases. The PS-OCT system revealed an increase of the optical scattering coefficient ($p<0.1$) and elevated backscattering/scattering ratio in both AD and CTE brain samples, compared to NC. To understand the underlying causes of the changes in optical properties, the high-resolution BRM imaging provided further insights, demonstrating that these changes in optical parameters were associated with damaged myelinated axons, leading to fragmented and disoriented myelin structures. Our findings suggest that myelin degradation has the potential to serve as a valuable biomarker for AD and CTE, contributing significantly to alterations in optical scattering within brain tissue. Notably, the severity of myelin degradation appeared to be more pronounced in CTE compared to AD, which could be attributed to repeated head trauma in CTE cases. Importantly, the lower-resolution PS-OCT system we employed allows for label-free volumetric imaging of large samples, offering a more efficient and cost-effective alternative to routine pathological assessment. This imaging technique holds promise as a valuable tool for future research endeavors, aiding in the understanding of the underlying mechanisms of neurodegenerative diseases such as AD and CTE.

**Disclosures:** **A. Novoseltseva:** None. **J. Yang:** None. **S. Chang:** None. **N. Blanke:** None. **G. Kureli:** None. **P. Antinew:** None. **B. Qiu:** None. **A. Chen:** None. **H. Wang:** None. **I. Bigio:** None. **D. Boas:** None. **A. McKee:** None.

**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.09/Web Only

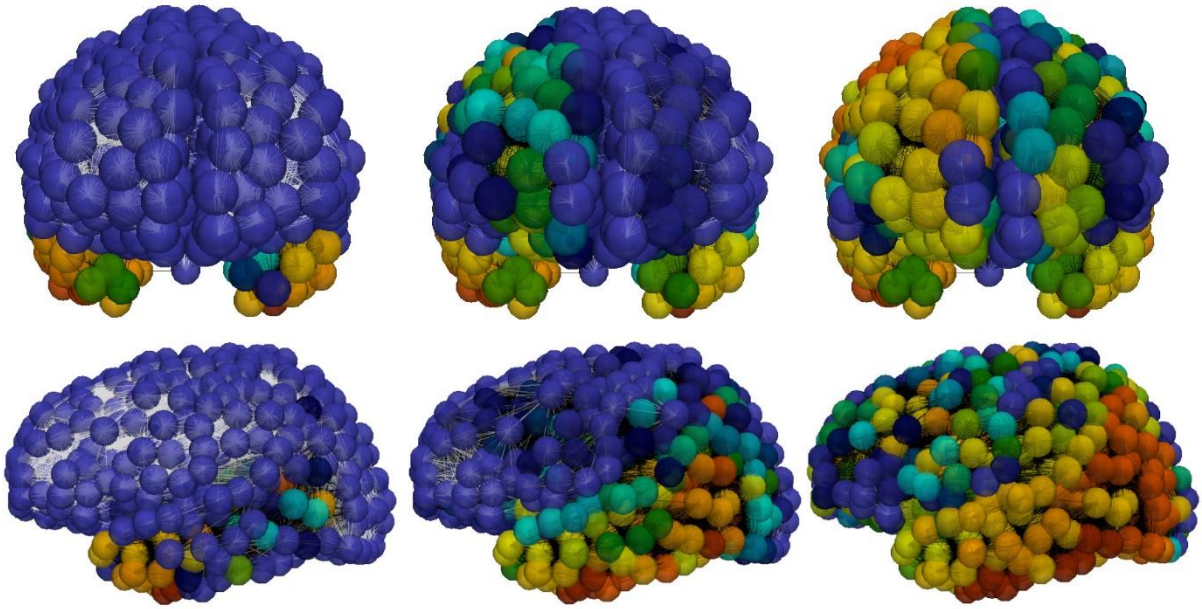
**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** EPSRC EP/L015803/1
EPSRC EP/R020205/1

**Title:** Mathematically modelling Alzheimer's disease; the role of clearance in neurodegeneration

**Authors: *G. S. BRENNAN**[1], T. B. THOMPSON[2], H. OLIVERI[1], M. E. ROGNES[3], A. GORIELY[1];
[1]Univ. of Oxford, Oxford, United Kingdom; [2]Texas Tech. Univ., Lubbock, TX; [3]Simula Res. Lab., Oslo, Norway

**Abstract:** Every day, over 28,000 people are diagnosed with dementia, making it a leading cause of death and economic burden worldwide. The most common form of dementia is Alzheimer's disease (AD). Insights gathered from experiments have highlighted the fundamental importance of the brain's clearance mechanisms in the potential onset and trajectory of tauopathy and a relationship between impaired brain clearance and increased concentrations of toxic proteins. In response to clinical observations, our research delivers the first mathematical model of coupled brain clearance and AD progression, and our data-driven computational approach simulates 40 years of AD progression on a network model of the human brain in less than 14 seconds of computational time (see Figure of simulated clearance-mediated spreading of tau through a human brain). We use a reaction-diffusion dynamical system to yield theoretical insights into the neurodegeneration process and its coupled relationship with brain clearance. Computational results, on high-resolution brain graphs constructed from the data of 426 patients, suggest that clearance deficits do indeed play an important role in neurodegeneration. A key finding is that the coupling between proteopathic spreading and regional brain clearance may not only alter the trajectory of AD but also provide a potential window into understanding AD subtypes. Further, we extract and analyse regional clearance rates on the brain network from the human gadobutrol tracer intensity data of Eide et al (2021). We apply this human CSF-ISF-mediated clearance data to our mathematical model, which highlights the potential impact of sleep deprivation, and heterogeneity in regional brain clearance, on advancing AD pathology. Mathematical modelling of AD offers an avenue for safe, ethical, and cost-effective in-silico experimentation and exploration of the role of clearance in AD pathology.



**Disclosures:** **G.S. brennan:** None. **T.B. Thompson:** None. **H. Oliveri:** None. **M.E. Rognes:** None. **A. Goriely:** None.

**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.10/E39

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

**Support:** NIH R01NS072497

**Title:** Astrocytic endfeet power CSF flow in perivascular space: a simulation study

**Authors: *A. KOLKO**[1], C. MEINHART[2], L. R. PETZOLD[2], X. ARAKAKI[3];
[1]Mechanical Engin., [2]UC Santa Barbara, Santa Barbara, CA; [3]Huntington Med. Res. Inst., Pasadena, CA

**Abstract:** The glymphatic system, generally thought to be a system for waste clearance and other functions, consists of a system of interconnected perivascular spaces carrying cerebrospinal fluid (CSF) bordered by astrocytic vascular endfeet that express the water channel aquaporin-4 (AQP4) [1]. The current understanding of perivascular CSF flow is that a peristaltic flow is driven by secondary effects of blood pressure. However, this understanding remains incomplete, as it is unclear what mechanisms produce a net flow of CSF in the perivascular space[2]. We propose that a potential biasing in flow direction is created by the efflux of CSF into astrocyte end-foot gaps in addition to aquaporin 4 channels, which expand upon positive pressure and contract under negative pressure. Using a finite element model in COMSOL Multiphysics, we examine the possibility of both elliptical and circular cross-sectional end-foot gap shapes, and demonstrate their potential roles in producing a net flow of CSF in the direction of blood flow. The results suggest that normal astrocytic endfeet function may be critical in net CSF flow in healthy individuals. Endfeet dysfunction may result in insufficient net CSF flow and waste removal from the brain parenchyma, compromising brain homeostasis in neurological disorders such as Alzheimer’s disease or migraine.[1] Jessen NA, Munk AS, Lundgaard I, Nedergaard M. The Glymphatic System: A Beginner's Guide. Neurochem Res. 2015 Dec;40(12):2583-99. doi: 10.1007/s11064-015-1581-6. Epub 2015 May 7. PMID: 25947369; PMCID: PMC4636982.[2] Tomas Bohr, Poul G. Hjorth, Sebastian C. Holst, Sabina Hrabětová, Vesa Kiviniemi, Tuomas Lilius, Iben Lundgaard, Kent-Andre Mardal, Erik A. Martens, Yuki Mori, U. Valentin Nägerl, Charles Nicholson, Allen Tannenbaum, John H. Thomas, Jeffrey Tithof, Helene Benveniste, Jeffrey J. Iliff, Douglas H. Kelley, Maiken Nedergaard, The glymphatic system: Current understanding and modeling, iScience, Volume 25, Issue 9, 2022, 104987, ISSN 2589-0042,

**Disclosures:** **A. Kolko:** None. **C. Meinhart:** None. **L.R. Petzold:** None. **X. Arakaki:** None.

**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.11/E40

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

**Support:** NIH R01NS115401

**Title:** Early changes in cerebrovascular reactivity and its relationship to cerebral microcirculation and oxygenation in a CADASIL mouse model

**Authors: *P. SHIN**[1], Q. PIAN[1], B. FU[1], Z. STARKWEATHER[1], S. A. CARP[1], M. A. FRANCESCHINI[1], S. A. VINOGRADOV[2], T. LONGDEN[3], T. SECOMB[4], A. JOUTEL[5], M. T. NELSON[6], C. AYATA[1], S. SAKADZIC[1];
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**Abstract:** Cerebral autosomal dominant arteriopathy and subcortical infarcts and leukoencephalopathy (CADASIL) is the most common monogenic inherited form of small vessel disease (SVD) leading to dementia, caused by mutations in *NOTCH3*. CADASIL shares many of the clinical and pathological features of sporadic forms of SVD, albeit its prevalence is known to be much lower among SVDs. However, we still lack understanding of how functional vascular changes in SVD are linked to cerebral microcirculation and oxygenation. Here, we performed multimodal optical imaging of cerebral microcirculation, oxygenation, and relative cerebral blood volume in a clinically relevant mouse model of CADASIL longitudinally over months. We showed that CADASIL leads to abnormal hemodynamic response to functional activation at an early age of 4 months and impaired hemodynamic response to mild hypercapnia at an even earlier age of 3 months. These impairments were followed by gradual decreases in the mean capillary RBC flux and pO2 over 4 months. All measurements were performed in awake mice. Altogether, these data suggest a gradual increase in microvascular dysfunction causing a mismatch between oxygen supply and demand that may eventually lead to tissue hypoxia in CADASIL. These results also suggest a step towards a targeted CADASIL therapy by providing guidelines about the timing of treatments at various stages of the disease.

**Disclosures: P. Shin:** None. **Q. Pian:** None. **B. Fu:** None. **Z. Starkweather:** None. **S.A. Carp:** None. **M.A. Franceschini:** None. **S.A. Vinogradov:** None. **T. Longden:** None. **T. Secomb:** None. **A. Joutel:** None. **M.T. Nelson:** None. **C. Ayata:** None. **S. Sakadzic:** None.

**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.12/E41

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

**Support:** NIH Grant DA035714
NIH Grant DA047924
NIH Grant DA057866
JSPS Grant 22H02962
JSPS Grant L23548

**Title:** In vitro HIV-1 Tat protein exposure alters the morphological characteristics in the primary mouse cortex endothelial cells and gene expression in human brain microvascular endothelial cells

**Authors: *J. ZHU**[1,2], L. QUAN[2], R. MURAMATSU[2];
[1]Drug Discovery and Biomed. Sci., Col. of Pharmacy, Univ. of South Carolina, Columbia, SC;
[2]Mol. Pharmacol., Natl. Inst. of Neuroscience, Natl. Ctr. of Neurol. and Psychiatry, Kodaira, Tokyo, Japan

**Abstract:** HIV-1-associated neurocognitive disorders (HAND) are highly prevalent in the era of combination of antiretroviral therapies. Recent study suggests that the damage of blood-brain barrier (BBB) is an early biomarker of human cognitive dysfunction. The BBB is a target site of entry for HIV-1 virus and HIV-infected monocytes and macrophages that can traverse the BBB either paracellularly or transcellularly. Particularly, HIV-1 viral proteins can attack tight junctions at the BBB and directly compromise its integrity, resulting in the entry of the virus into the brain. This study determined the effects of HIV-1 transactivator of transcription (Tat) protein on the morphological profiles of primary mouse cortex endothelial cells and the endothelial cell-mediated gene expression. The cortex endothelial cells were isolated from three-month-old C57BL/6J mice and exposed to 12.5 nM recombinant $Tat_{1-86}$ ($rTat_{1-86}$) for 6, 12, 24, or 48 hours, respectively. The cells were subsequently immunostained with CD31 as a marker for endothelial cells, anti-Tat, DAPI or phalloidin for labeling actin filaments and harvested for RNAseq. Results show that 48-hour Tat exposure reduced the CD31-positive endothelial cells and increased immunofluorescence staining of phalloidin. Moreover, the phalloidin staining showed that actin cytoskeleton structure was disrupted in the endothelial cells after 48-hour Tat exposure. In a separate study, human brain microvascular endothelial cells were exposed to 12.5 nM $rTat_{1-86}$ for 8 hours and subsequently gene expression was analyzed by RNAseq. We found that 72 genes were upregulated, and 21 genes were downregulated. Ongoing studies are to test whether *in vivo* Tat expression in inducible Tat transgenic mice replicates the *in vitro* Tat-induced morphological changes and whether Tat and cocaine synergistically exacerbate the Tat's effect on endothelial cells. These findings highlight a role for the HIV-1 Tat protein in the compromise of BBB integrity, a critical feature of HAND development.

**Disclosures: J. Zhu:** None. **L. Quan:** None. **R. Muramatsu:** None.

**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.13/F1

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

**Support:** DCCFAR GR414738

**Title:** Mu opioid receptor activation does not activate hiv provirus transcription in a microglia model of latent hiv infection

**Authors: *M. K. B. BECHER**[1], L. A. CAMPBELL[2], U. KANTH[1], I. MOCCHETTI[1]; [1]Georgetown Univ. Med. Ctr., Georgetown, DC; [2]Georgetown Univ., Washington, DC, DC

**Abstract:** The increased use of dangerous opioids such as fentanyl have been observed in this current opioid epidemic. Infection of Human immunodeficiency virus (HIV) is a common co-morbibity with people who inject drugs. HIV infection can lead to the development of HIV associated neurocognitive disorder (HAND), even in the age of antiretroviral therapy. HAND is triggered by the infection of immune cells, including microglia, which creates a reservoir for HIV in the brain. Infected microglia can in turn elevate the inflammatory response in the brain and damage surrounding neurons. Thus, it is important to understand if opoids will enhance the progression of HAND. In order to investigate the role of opioids on HIV transcription through microglia, we used a human microglia-like cell line which contains a stably integrated, and non-replicative HIV provirus with a luciferase-based reporter (HIV-NanoLuc CHME-5 E9). To determine whether these cells express opioid receptors, we analyzed mu and delta opioid receptor immunoreactivity by both immunohistochemistry as well as Western blot, which showed that the receptors are indeed expressed in these cells. Exposure of this cell line to various concentrations of opioids, such as Fentanyl and Methadone, did not change luciferase activity up to 24 hr. These results were also confirmed with a surface biotinylating assay, showing that the delta receptor was internalized by exposure to fentanyl, while the mu receptor was not. Thus, it appears that opioids do not affect HIV transcription in our model of HIV infection of microglia. As a positive control of the experiments, cells were exposed to LPS, a TLR4 agonist that directly increase transcription of HIV through its ability to increase the transcription factor of NF-kappaB. LPS significantly increased luminescence within 24 hr, proving the HIV promoter in this model can be activated. These results show that both fentanyl and methadone minimally activate transcription of the HIV provirus. Together, these results suggest that in our model of HIV infection in microglia, opioids that act on mu opioid receptors do not increase transcription of HIV. Therefore, we suggest that commonly prescribed and abused opioids do not enhance activation of transcription of HIV, indicating that therapy with methadone might be a suitable avenue for treating addiction in people living with HIV.

**Disclosures: M.K.B. Becher:** None. **L.A. Campbell:** None. **U. Kanth:** None. **I. Mocchetti:** None.

**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.14/Web Only

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

**Support:** The establishment of university fellowships towards the creation of science technology innovation

**Title:** Skeletal muscle atrophy reduces cognitive function in young normal mice

**Authors: *T. IKI**[1], C. TOHDA[2];
[1]Univ. of Toyama, Toyama, Japan; [2]Inst. of Natural Medicine, Univ. of Toyama, Toyama, Japan

**Abstract:** Decline in physical movement with aging is supposed to a cause of age-associated lowering of the brain function. However, no direct evidence showed that skeletal muscle atrophy caused cognitive decline. Our previous study revealed that the skeletal muscle atrophy shifted the onset of memory dysfunction earlier without increasing the deposition of amyloid-beta in young mice model of Alzheimer's disease (AD). The atrophied muscles secreted hemopexin, and i.c.v. infusion of hemopexin induced cognitive impairment in young AD model and wild-type mice. This indicates the possibility that hemopexin is directly involved in the onset of cognitive impairment. However, these data were obtained in familial AD model mice, so that it was complicated only muscle atrophy was predisposing factor for the onset. This study aimed to elucidate the onset of the skeletal muscle atrophy-driven memory impairment and establish a new strategy to prevent cognitive impairment by approaching skeletal muscle hemopexin. Normal mice (ddY, 11-13 weeks old) were used. To investigate effects of skeletal muscle atrophy specifically, we used young mice rather than aged or accelerated senescence mice. The bilateral hindlimbs were immobilized by cast-attachment for 14 days. After the cast immobilization, wet weights of tibialis anterior and triceps surae were significantly lower in cast-attached mice than those in non-cast mice. At the same time, object recognition memory in the cast-attached mice was impaired although in age-matched non-cast mice showed normal memory function. The hindlimb muscles were isolated for organ culture, and conditioned media (CM) was collected. Hemopexin levels in the CM, skeletal muscle and hippocampus were increased in cast-attached mice. To investigate the neuronal activity after increasing hemopexin concentration in the brain, we are currently measuring the expression level of c-Fos using primary cultured hippocampal neurons. We are investigating prevention of memory deficit by hemopexin antisense oligo injected mice. These evidences indicate that skeletal muscle atrophy induces cognitive impairment in young non-AD mice, and hemopexin secreted from skeletal muscle is possibly involved in the phenomenon.

**Disclosures: T. Iki:** None. **C. Tohda:** None.

**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.15/F2

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

**Support:** NIH R61NS115161

**Title:** Loss of TDP-43 in neurons exacerbates neurodegeneration through accelerated tauopathy in a mouse model of mixed etiology dementia

**Authors: *M. BAGHEL**[1], T. LI[2], P. C. WONG[2,3];
[1]Johns Hopkins Med. Institutions, Baltimore, MD; [2]Pathology, [3]Neurosci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

**Abstract:** Alzheimer's disease (AD)-Related Dementias is a group of progressive neurodegenerative disorders with mid to late life onset, including Lewy body dementia, frontotemporal dementia (FTD) or mixed etiology dementia (MED) such as AD exhibiting TDP-43 pathology. In efforts to clarify disease mechanisms and identify therapeutic targets for this disorder, a critical need is the availability of new multi-dimensional mouse models that replicate combinations of co-occurring pathological features of human dementia. Recent studies indicate that TDP-43 proteinopathy, initially associated with amyotrophic lateral sclerosis and FTD, is also found in 30-60% of AD cases and correlates with worsened neurodegeneration and cognitive functions. How TDP-43 pathology contributes to neuron loss and cognitive deficits remains elusive. Our previous work supporting the view that loss of TDP-43 splicing repression of cryptic exons underlies neurodegeneration led us to hypothesize that in MED, loss of such TDP-43 function exacerbates AD pathologies and/or neuron loss. To address this question, we generated a mouse model for MED (*APPswe/PS1ΔE9;Tau4R;CaMKIIα$^{ER}$;TDP-43$^{F/F}$*) by a crossbreeding strategy with our previously characterized inducible model lacking TDP-43 in forebrain neurons (*CaMKIIα$^{ER}$;TDP-43$^{F/F}$*) and inducible tau (*Tau4R*) and β-amyloidosis (*APPswe/PS1ΔE9*) mouse models. To test the influence of TDP-43 on tauopathy-dependent neurodegeneration, we deleted TDP-43 temporally in excitatory hippocampal neurons through oral administration of tamoxifen citrate for 4 weeks in 12 month-old "MED" mice as well as *CaMKIIα$^{ER}$;TDP-43$^{F/F}$* and *APPswe/PS1ΔE9;Tau4R* control littermates and these mice were subsequently sacrificed and analyzed at 20-month of age. As expected for *CaMKIIα$^{ER}$;TDP-43$^{F/F}$*, we observed selective vulnerability of CA2/3 neurons. As compared to control mice, such vulnerability is exacerbated in the MED model. Interestingly, we found a marked loss of granule neurons in the dentate gyrus and CA1 subregion of hippocampus of MED mice. We characterized the pathological conversion of endogenous tau using immunohistochemistry and observed that, as compared to control littermates, TDP-43 loss in MED mice accelerated the pathological conversion of endogenous tau. Thus, these intriguing observations are consistent with the idea that loss of TDP-43 function accelerates tauopathy-dependent neuron loss in AD exhibiting TDP-43 pathology and this novel mouse model holds promise as a faithful mimic for this type of MED.

**Disclosures: M. Baghel:** None. **T. Li:** None. **P.C. Wong:** None.

**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.16/F3

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

**Support:** KBRI 23-BR-02-04
the Ministry of Health & Welfare and Ministry of Science and ICT
HU21C0027

**Title:** Identification of Picalm as a novel regulator of TDP-43

**Authors: *J. LEE**[1,2], J. KIM[2];
[1]Kyungpook Natl. University, KBRI, Daegu, Korea, Republic of; [2]KBRI, Daegu, Korea, Republic of

**Abstract:** Transactive response (TAR) DNA-binding protein 43 (TDP-43) is widely expressed nuclear protein which regulates the expression of a variety of genes via regulating RNA splicing, trafficking, and/or stabilization. Under pathological context, TDP-43 is mislocalized to cytoplasm and aggregated into insoluble inclusions, leading to neurodegeneration in various neurodegenerative diseases, such as Amyotrophic lateral sclerosis (ALS), Frontotemporal dementia (FTD), and Alzheimer's disease (AD). However, our understanding of the pathological mechanisms of TDP-43 proteinopathies remains elusive. Therefore, it is critical to identify the regulation mechanisms of TDP-43 pathology to develop novel therapeutic interventions. To identify a novel regulation of TDP-43 expression, we developed a cellular model of TDP-43 proteinopathies using neuronal cells. Using this cellular model, we identified Phosphatidylinositol binding clathrin assembly protein (Picalm) as a novel regulator of TDP-43 expression. We validated that the protein levels of Picalm is dramatically decreased upon TDP-43 overexpression. Furthermore, we demonstrated that overexpression of Picalm strongly suppressed the TDP-43 expression. Our data suggest that Picalm is a novel regulator of TDP-43 expression and may represent a novel therapeutic targets for TDP-43 proteinopathies. In the further study, we will dissect how Picalm regulates TDP-43 expression.

**Disclosures:** **J. Lee:** None. **J. Kim:** None.

**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.17/F4

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

**Support:** Syncell Spatial Proteomics Pilot Award

**Title:** Discovery optoproteomics of de novo pathological aggregates from human TDP-43 proteinopathies

**Authors: *M. C. WREN**[1,2], D. MORDERER[1], C.-C. HUANG[4], J.-C. LIAO[4], D. W. DICKSON[1], *M. C. WREN[3], W. ROSSOLL[1];
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**Abstract:** TAR DNA-binding protein-43 (TDP-43) pathology is characterized by the mislocalization of the protein from the nucleus into cytoplasmic deposits where it undergoes hyperphosphorylation, ubiquitination and proteolytic fragmentation. The presence of large phospho-TDP-43 (pTDP-43) positive aggregates is the major neuropathological hallmark in ~97% of ALS and ~50% of FTD cases, two progressive and devastating neurodegenerative disorders with overlapping genetic, clinical, and histopathological features. TDP-43 pathology can be classified into distinct subtypes based on the distribution and morphology of the aggregates, but the composition of the aggregates and the nature of these differences remains unknown. As a limitation of current technologies, the in-depth characterization of neuropathologic TDP-43 inclusions has historically been difficult to address, since these aggregates are detergent-insoluble, and thus refractory to classical affinity purification methods. Current cellular and animal models of TDP-43 pathology do not authentically replicate aggregate formation and spread observed in human pathological disease entities and are therefore not suitable to address this important question. To address the limitation of current approaches, we are using the novel spatial proteomics method developed by Syncell for the proximity-labeling, purification, and proteomic profiling of pathological TDP-43 aggregates from fixed human patient tissue, using both sporadic and familial FTD/ALS cases with abundant pTDP-43 pathology. The Microscoop system facilitates optical biotinylation of cytoplasmic pTDP-43 structures using patented nano-laser technology and guided by AI-trained image processing. Purification of the isolate has been analyzed by quantitative mass-spectrometry to obtain the first de novo pathological TDP-43 proteomes from human brain of over 450 proteins. Future studies aim to focus on the differences between FTD/ALS diseases with morphologically divergent patterns of TDP-43 pathology and candidates will be validated in larger post-mortem cohorts, to determine the functional roles of these aggregate-associated proteins in TDP-43 mislocalization and aggregation. This knowledge will be critical for developing new biomarkers and therapeutic strategies to track and target aberrant phase separation in ALS/FTD and other devastating neurodegenerative disorders with TDP-43 proteinopathy.

**Disclosures:** **M.C. Wren:** 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.; Syncell Inc. **D. Morderer:** 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.; Syncell Inc. **C. Huang:** A. Employment/Salary (full or part-time); Syncell Inc. **J. Liao:** A. Employment/Salary (full or part-time); Syncell Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Syncell Inc. **D.W. Dickson:** None. **M.C. Wren:** None. **W. Rossoll:** 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.; Syncell Inc.

**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.18/F5

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

**Support:** NIH Grant P30AG066507

**Title:** Loss of TDP-43 splicing repression is an early deficit that correlates with cognitive decline and Alzheimer's disease neuropathologic changes in the aging population

**Authors: *K. CHANG**[1], J. REDDING-OCHOA[1], Y. AN[3], L. LI[4], T. PYLYUKH[1], A. BARRETT[1], K. IRWIN[1], J. P. LING[1], P. C. WONG[1], A. MOGHEKAR[2], S. M. RESNICK[3], J. C. TRONCOSO[1];
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**Abstract:** TDP-43 neuropathologic changes are associated with Alzheimer’s disease (AD) and cognitive impairment in older adults. Whether loss of TDP-43 function occurs early in the aging brain is unknown. The association of TDP-43 proteinopathy with Alzheimer’s disease neuropathologic changes (AD-NC) and its contribution to decline in different cognitive domains in the aging population are not fully understood. We assessed TDP-43 neuropathologic changes and AD-NC in 309 autopsied brains from the Baltimore Longitudinal Study of Aging (BLSA) and 24 autopsied brains from a younger forensic cohort. We show that nuclear clearance of TDP-43 and TDP-43 loss-of-function judged by inclusion of cryptic exons occurs since 50s, preceding by a decade the appearance of the earliest TDP-43+ neuronal cytoplasmic inclusions (NCIs). Accumulation of a cryptic exon-encoded neoepitope is observed in neurons exhibiting nuclear clearance of TDP-43. In the BLSA participants, age at death, female sex, high CERAD NP score, and high Braak NF stage significantly increase the odds of TDP-43+ neuronal cytoplasmic inclusions (NCIs) presence. Using linear mixed effects models, TDP-43+ NCIs positivity showed significant association with the cognitive trajectories of California Verbal Learning Test (CVLT) immediate recall, Card Rotation Test, MMSE and category fluency test. The associations of TDP-43+ NCIs positivity with CVLT immediate recall (memory function) and Card Rotation (visual-spatial function) Test remain significant after adjusting for AD-NC. This study shows that loss of TDP-43 function is preceded the aggregates of TDP-43 protein in the NCIs, and TDP-43 proteinopathy is associated with the decline of memory and visuo-spatial ability in the aging population and that this association is independent of AD.

**Disclosures:** **K. Chang:** None. **J. Redding-Ochoa:** None. **Y. An:** None. **L. Li:** None. **T. Pylyukh:** None. **A. Barrett:** None. **K. Irwin:** None. **J.P. Ling:** None. **P.C. Wong:** None. **A. Moghekar:** None. **S.M. Resnick:** None. **J.C. Troncoso:** None.

**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.19/F6

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

**Support:** AMED JP23dm0207116
JSPS KAKENHI Grant Number 23K16817

**Title:** Development of translatable indicator between humans and marmosets for early diagnosis of Frontotemporal lobar degeneration(FTLD)and Amyotrophic lateral sclerosis (ALS)

**Authors: *Y. KIM**[1], K. ENDO[2], J. HATA[3], K. NAKAMURA[4], S. ISHIGAKI[1];
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**Abstract:** Frontotemporal lobar degeneration (FTLD) is a type of dementia characterized by degeneration of the frontal lobes, temporal lobes, and basal ganglia, with clinical features such as loss of cognitive function, behavioral changes such as compulsivity, and personality changes. On the other hand, amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that affects the motor system and causes progressive muscle weakness, including respiratory muscle weakness, but also shows compulsive tendencies, as in patients with FTLD. Despite these two diseases have different clinical features, there is overlap regarding associated molecules and behavioral changes, such as compulsive tendencies. In this study, in order to develop a translatable indicator between humans and marmosets for FTLD/ALS, a probabilistic reversal learning (PRL) task was performed on humans and model marmosets. To generate FTLD/ALS model marmosets, fused in sarcoma (FUS), one of the common factors of FTLD and ALS was focused on. 90 ALS patients and 127 cognitively normal participants performed the PRL task. Data from 56 ALS patients and 60 control participants were valid. Based on these data, four indicators of heuristic learning strategies in PRL: "win-stay," "lose-shift," "win-shift," and "lose-stay were calculated and compared between 2 groups. In addition, participants performed MRI scans. These MRI data were conducted for VBM analysis and resting-state network analysis. As a result, there were no significant differences in scores on the PRL task between the ASL group and the control group. However, in a comparison of four indicators, the number of "lose-shifts" was significantly reduced overall, before and after a reversal in human ALS patients compared to healthy controls. For experiments with marmosets, we designed shRNAs against the marmoset FUS gene and generated an AAV9 virus encoding the most effective shRNA against FUS. The AAV encoding shFUS was introduced into the bilateral caudate heads of marmosets, whereas

AAV encoding randomized shRNA was injected as a control. Next, marmosets conducted a PRL task to investigate decision-making abnormalities. As a result, MRI analysis revealed that compared to control marmosets, the FUS-KD marmosets reduced neural connectivity between PFC and caudate nucleus. However, there were no significant differences between the two groups in PRL task scores and in the four indices. These results suggest that the PRL task can be used as a new index for early diagnosis of ALS patients. However, the PRL task for marmosets needs to be adjusted to be used as a translatable indicator between humans and marmosets.

**Disclosures: Y. Kim:** None. **K. Endo:** None. **J. Hata:** None. **K. Nakamura:** None. **S. Ishigaki:** None.

**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.20/F7

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

**Support:** AbbVie

**Title:** Multivalent antibody PHF1 generated to increase avidity and enable superior binding strength and selectivity to pathological tau species

**Authors: *H.-Y. WU**[1], B. LI[2], O. NAZARKO[2], X. YANG[2], L. BOUCHER[3], K. YANAMANDRA[4], E. MATTSON[2], M. QIAO[2], N. BROWN[2], K. TAYLOR[2], Z. DAI[2], R. IYER[3], X. LANGLOIS[4], Y. AKAMATSU[5], L. HUANG[2], A. GOODEARL[2];
[2]AbbVie Bioresearch Center, Biotherapeutics and Genet. Med. Technologies, [1]Abbvie, Worcester, MA; [3]Biologics Discovery and Science, Biotherapeutics and Genet. Med. Technologies, Abbvie, Lake County, IL; [4]AbbVie Foundational Neurosci. Ctr., Abbvie, Cambridge, MA; [5]AbbVie Bay Area, Biotherapeutics and Genet. Med. Technologies, Abbvie, South San Francisco, CA

**Abstract:** Immunotherapy targeting tau has emerged as a promising therapeutic strategy to provide disease-modifying treatment for Alzheimer’s disease (AD) and other tauopathies. A number of monoclonal antibodies have reached AD clinical trials. However, no effective antibody therapy has been approved thus far. Therefore, searching for exceptional strong binders to pathological tau is still needed. Binding affinity and potency of antibodies to multimeric targets such as aggregated tau can be greatly enhanced by avidity. Here, we generated monovalent, bivalent, and tetravalent tau antibodies and investigated if increased valency improves sensitivity and efficacy of a tau antibody to pathological tau species. PHF1, a monoclonal antibody selectively binding to pathologically phosphorylated tau at S396/404, was used as the parent antibody. We have created a tetravalent PHF1 to increase avidity through recombinant fusion of single chain variable fragments of PHF1 to the N-terminal ends of PHF1 heavy chains, forming a novel tetravalent molecule called TetraPHF1. We were able to produce

this TetraPHF1 at high yield and purity similar to its parent PHF1, without compromising biophysical properties required for effective drug development. To reduce the valency of PHF1, we also engineered a monovalent PHF1 antibody called AB095PHF1 by replacing one arm of the PHF1 Fabs with sequences that does not recognize tau. Surface Plasmon Resonance (SPR) and ELISA demonstrated that, compared to the bivalent parent PHF1, TetraPHF1 had much stronger binding to both recombinant phosphorylated tau aggregates and human AD brain MC1-immunopurified tau species, while retaining intermediate binding to tau phosphorylated monomers and a pS396 containing tau peptide (20 aa in length). AB095PHF1 showed diminished binding compared to both TetraPHF1 and the parent PHF1, suggesting a crucial role of avidity for tau aggregate binding of PHF1. In addition, we observed that TetraPHF1 mediated significantly higher levels of tau aggregate uptake in N9 and SIM A9 microglia cells than observed for the bivalent parent. This result was supported by in-solution complexation and SEC-MALS analysis where TetraPHF1 formed higher order complexes than the parent PHF1. Furthermore, *in vitro* immunoprecipitation with human AD brain lysate, SIMOA analysis, and seeding study in tau biosensor cells indicated that TetraPHF1 immuno-depleted more seeding competent tau compared to its parent PHF1. Together, this study introduces a novel multivalent design of anti-tau antibody with increased valency to promote binding avidity to pathological tau species.

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**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.21/F8

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

**Title:** Inhibiting dipeptide repeat propagation in C9-ALS

**Authors: *S. C. AKERMAN**[1], O. SPEAD[2], B. L. ZAEPFEL[4], M. HUANG[5], A. G. THOMAS[6], C. TALLON[2], B. S. SLUSHER[7], J. D. ROTHSTEIN[3];
[1]Neurol., [2]Brain Sci. Institute/Neurology, [3]Johns Hopkins Univ., Johns Hopkins Univ., Baltimore, MD; [4]Neurol., [5]Brain Sci. Institute/Neurology, Johns Hopkins, Baltimore, MD; [6]Johns Hopkins Drug Discovery, Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [7]Johns Hopkins Drug Discovery, Baltimore, MD

**Abstract:** Amyotrophic Lateral Sclerosis (ALS) is a devastating neurodegenerative disease affecting both upper and lower motor neurons. Clinical studies indicate that ALS can start focally and then spread within the spinal cord and in the cortex. Multiple lines of evidence indicate that the disease-causing mutant proteins identified in ALS patients, such as C9orf72-

associated dipeptide repeats (DPRs), superoxide dismutase 1, or transactive response DNA-binding protein 43, and can form aggregates and these aggregates can spread from cell-to-cell in different ALS models. Understanding how these proteins propagate in ALS models can reveal novel therapeutic targets that can potentially slow down or halt this propagation. One way cell-to-cell communication occurs is through extracellular vesicles (EVs). Exosomes are a major type of EVs that are derived from the endosomal pathway through the formation of intraluminal vesicles that occur with negative curvature of the endosomal membrane.
Interestingly, several studies have identified an increase in sphingomyelin (SM) and ceramide in either ALS patients or transgenic mice models. Ceramide is an integral component of exosomal membranes. A major source of ceramide production is through the hydrolysis reaction of SM by the action of neutral sphingomyelinase 2 (nSMase2). Inhibition of exosome biogenesis by nSMase2 both at genetic and pharmacological level, has been shown to halt amyloid-beta aggregation and tau propagation in different Alzheimer's Disease models. Interestingly, nSMase2 inhibition has also been shown to play a role in the production of amyloid-beta albeit independent of its involvement in EV production. We hypothesize that exosome-mediated secretion of DPRs is one of the major contributing factors to cell-to-cell propagation of these aggregates, although their role in causing cell injury remains unclear in patients as well as endogenous expressing models. Using an in vitro model system, we detected DPR species in isolated EV fractions, in agreement with the current literature. Preliminary experiments suggest that these DPRs can propagate into new recipient cells. Furthermore, using a non-competitive inhibitor against nSMase2 - phenyl(R)-(1-(3-(3,4-dimethoxyphenyl)-2,6-dimethylimidazo[1,2-b]pyridazin-8-yl)pyrrolidin-3-yl)-carbamate (PDDC) - in a C9-AAV mouse model suggests that nSMase2 inhibition has the potential to decrease DPR burden.

**Disclosures:** **S.C. Akerman:** None. **O. Spead:** None. **B.L. Zaepfel:** None. **M. Huang:** None. **A.G. Thomas:** None. **C. Tallon:** None. **B.S. Slusher:** None. **J.D. Rothstein:** None.

**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.22/G1

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

**Support:** Lundbeck Foundation

**Title:** Sortilin Inhibition with VES001 and Elevation of Progranulin as a Novel Therapeutic Approach in FTD-GRN and Other Neurodegenerative Diseases.

**Authors: *L. KLEM**[1], P. KLEIN[1], M. CASES-THOMAS[1], P. LITTLE[2,1], A. NYKJAER[3,1], M. KJOLBY[1,3];
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**Abstract: Title:** Sortilin Inhibition with VES001 and Elevation of Progranulin as a Novel Therapeutic Approach in FTD-GRN and Other Neurodegenerative Diseases.
**Authors:** Louise Klem, Pontus Klein, Manuel Cases-Thomas, Paul Little, Anders Nykjaer, Mads Kjolby.
**Aims**: Progranulin deficiency is associated with different neurodegenerative disorders, including GRN-related frontotemporal dementia (FTD-GRN), and is associated with exacerbated neuroinflammation. Heterozygote carriers of null GRN mutations have 50% PGRN levels relative to healthy controls. Vesper Bio has developed novel sortilin inhibitors for oral administration and are investigating the therapeutic potential within different neurodegenerative diseases. The lead candidate, VES001, will enter Phase 1 clinical trials Q4 2023.
**Methods and materials**: Characterization of VES001 included quantification of target affinity by Grating-Coupled Interferometry, competition binding with PGRN by flow cytometry, and PK/PD studies in different species. The PK/PD studies included two rat studies that a) quantified changes in plasma following a range of single doses of VES001, and b) quantified changes in plasma, CSF, and brain interstitial fluid following repeated administration of VES001 in a microdialysis experiment. Pharmacodynamic changes in PGRN were quantified relative to baseline levels.
**Results:** VES001 shows a high affinity for sortilin across multiple species and inhibits PGRN binding. VES001 was measured in all compartments. Single-dose VES001 administration increased plasma PGRN up to 1.5-fold, and repeated dosing increased progranulin in plasma, CSF, and brain PGRN ~2-fold with the selected dose-range. The vehicle groups did not show changes in PGRN.
**Conclusion**: Sortilin inhibition increases progranulin in different compartments and holds promise as a novel therapeutic approach to attenuate neuroinflammation and neurodegeneration for different neurodegenerative disorders, including FTD-GRN.
**Keywords**: sortilin, progranulin, neurodegeneration, neuroinflammation, FTD, FTD-GRN, PD, ALS, AD

**Disclosures:** **L. Klem:** A. Employment/Salary (full or part-time); Vesper Bio. **P. Klein:** A. Employment/Salary (full or part-time); Vesper Bio. **M. Cases-Thomas:** A. Employment/Salary (full or part-time); Vesper Bio. **P. Little:** A. Employment/Salary (full or part-time); Vesper Bio. **A. Nykjaer:** A. Employment/Salary (full or part-time); Vesper Bio. **M. Kjolby:** A. Employment/Salary (full or part-time); Vesper Bio.

**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.23/G2

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

**Support:** US National Institutes of Health U01-NS110437 (RV, BG, WJ)
RF1-AG071177 (RV, BG, WJ)
R01-AG080001 (RV, BG)

K99-AG078500 (GIH)
T32-GM132024 (KAO)
Department of Pathology and Laboratory Medicine, Indiana University School of Medicine (BG, RV)

**Title:** Cryo-em structures of amyloid beta and tau filaments in down syndrome

**Authors: *A. FERNANDEZ**[1], M. HOQ[2], G. I. HALLINAN[1], D. LI[2], S. BHARATH[2], F. VAGO[2], K. OZCAN[2], K. NEWELL[1], H. GARRINGER[1], W. JIANG[2], B. GHETTI[1], R. VIDAL[1,3];
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**Abstract:** Down syndrome (DS) is the most common and best-known chromosomal disorder in humans and the most frequent cause of intellectual disability of genetic origin, affecting about 6 million people worldwide. Individuals with DS may develop Alzheimer disease (AD) by age 55-60 years, and sometimes as young as 40 years due to the triplication of the amyloid β precursor protein (ABPP) gene, which is located on chromosome 21. The AD neuropathological phenotype observed in individuals with DS includes amyloid-β (AB) deposition (parenchymal and vascular) and neurofibrillary tangles (NFTs) comprised of tau protein. Aβ peptide species ending at 42 ($AB_{42}$) are the main component of senile plaques and diffuse deposits in AD and AD in DS, while Aβ peptides ending at position 40 ($AB_{40}$) are the predominant Aβ peptides found in both leptomeningeal and cortical vessels. Whether there is a difference in the structures of AB and tau filaments between AD in DS and AD, is unknown. The recent characterization by cryo-electron microscopy (cryo-EM) of the structure of AB and tau filaments in AD and related disorders allows researchers to gain further insights into similarities and differences between AD and AD in DS, by comparing the structure of AB and tau filaments between the two. Herein, we used cryo-EM to characterize AB and tau filaments extracted from the brain of two individuals with DS. Presence of AD pathology in both cases was neuropathologically confirmed. Trisomy 21 was verified by chromosomal microarray analysis on genomic DNA from brain tissue. We found two types of $AB_{42}$ filaments (I and II) identical to those found in sporadic and familiar AD and two novel $AB_{40}$ filaments that differ from those previously reported in sporadic AD. We also characterized the filamentous tau inclusions deposited in DS. Tau filaments (PHFs and SFs) were identical to those in AD, supporting the notion of a common mechanism through which amyloids trigger aggregation of tau. This knowledge is crucial for understanding AD in DS and assessing whether adults with DS could be included in AD clinical trials.

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**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.24/G3

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

**Support:** NIH Grant R25GM060507

**Title:** Neurosteroid Regulation of Mitochondrial Calcium Signaling in Niemann-Pick Type C Disease

**Authors: *K. L. SANCHEZ**, J. WHITE, A. TOLAN, S. SORIANO;
Human Anat., Loma Linda Univ., Loma Linda, CA

**Abstract:** Niemann-Pick Disease type C (NPC) is a rare neurodegenerative disorder caused by mutations in the genes *Npc1* or *Npc2*, with Npc1 accounting for 95% of cases. The *Npc1* and *Npc2* genes encode for the NPC1 and NPC2 proteins, respectively, which are believed to be responsible for the transport of cholesterol from the late-endosome/lysosome to other compartments of the cell. Loss of function of these proteins results in intracellular cholesterol accumulation, calcium dysregulation, oxidative stress, lipid peroxidation and a proinflammatory environment. The mechanisms by which these pathological hallmarks are linked within a pathogenic network are not well understood. Within the brain, cerebellar Purkinje cells are particularly sensitive to NPC1 mutations. Purkinje cells, GABAergic inhibitory neurons, are the sole output from the cerebellum, and they serve multiple functions to optimize motor coordination, learning, memory and, uniquely, they are one of the few cells with neurosteroidogenic properties. Within Purkinje cells, neurosteroid synthesis occurs in the mitochondrial inner membrane and relies on cholesterol as a precursor. *Npc1*$^{-/-}$ models demonstrate a decrease in neurosteroid synthesis, due to unavailability of cholesterol. This is significant because neurosteroids play a critical role in mitochondria by regulating $Ca^{2+}$ homeostasis. Accordingly, we hypothesize that impaired neurosteroidogenesis in Purkinje cells may contribute to cell death in NPC through dysregulated calcium signaling in mitochondria which would exacerbate oxidative stress resulting in lipid peroxidation and a proinflammatory environment. To address our hypothesis, we utilized a genome-wide cerebellum transcriptome analysis of pre-symptomatic *Npc1*$^{-/-}$ mice and age-matched wild-type mice, and we report that, indeed, there are significant differences in the expression of genes involved in neurosteroidogenic and calcium homeostasis pathways between healthy and *Npc1*$^{-/-}$ mice. Because these differences occur prior to disease onset, our findings support a causative role for neurosteroid synthesis dysregulation and mitochondrial $Ca^{2+}$ dyshomeostasis in NPC pathogenesis.

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**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.25/G4

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

**Support:** McDonnell Center for Systems Neuroscience Small Grants Program
McDonnell International Scholars Academy, Washington University in St. Louis
Noah's Hope/Hope for Bridget
Department of Pediatrics, Washington University in St. Louis

**Title:** Defining the contribution of GABAergic interneuron deficits to epileptogenesis in neurodegenerative lysosomal storage disorders

**Authors: K. TAKAHASHI**, E. M. EULTGEN, S. H. WANG, H. R. NELVAGAL, N. R. RENSING, E. B. HAN, M. WONG, M. S. SANDS, *J. D. COOPER;
Pediatrics, Washington Univ. Sch. of Med., Saint Louis, MO

**Abstract:** Dysfunction or loss of GABAergic inhibitory neurons has been implicated in the epileptogenesis of multiple neurodegenerative diseases. Our recent work has revealed a fatal seizure phenotype in *Cln2*$^{R207X}$ mice, which models CLN2 disease, a common form of childhood-onset neurodegenerative disorders called neuronal ceroid lipofuscinoses (NCLs). CLN2 disease is caused by a deficiency of the soluble lysosomal enzyme TPP1. These mice display an early loss of several cortical inhibitory neuron populations including those positive for parvalbumin, somatostatin and calbindin, although those neurons in the hippocampus are relatively spared. These findings led us to hypothesize that cortical interneuron loss may contribute to the epileptogenesis associated with CLN2 disease. We have been investigating this hypothesis using two complimentary strategies. Firstly, we selectively enhanced interneuron activities in *Cln2*$^{R207X}$ mice using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs). This was achieved by orally administrating the novel DREADD ligand, deschloroclozapine (DCZ), to *Vgat-Cre*: *Cln2*$^{R207X}$ mice expressing *Cre*-dependent hM3Dq. Longitudinal EEG monitoring has shown that chronic DCZ administration exacerbated spontaneous seizures and interictal abnormalities in the hM3Dq-expressing *Vgat-Cre*: *Cln2*$^{R207X}$ mice compared to the control mCherry-expressing *Vgat-Cre*: *Cln2*$^{R207X}$ mice, suggesting that modulating interneuron activity can exert influence over epileptiform abnormalities in CLN2 disease. Secondly, we have generated interneuron-specific *Cln2*$^{R207X}$ mice using our transgenic mice expressing hTPP1 tethered to the transmembrane portion of lysosomal associated membrane protein 1 (LAMP1). This TPP1LAMP1 fusion protein is biologically active but not secreted extracellularly, allowing us to study the cell-autonomous effects of TPP1 deficiency *in vivo*. After confirming that homozygous expression of *LoxP*-flanked TPP1LAMP1 rescued neuropathological and behavioral abnormalities of *Cln2*$^{R207X}$ mice, we have crossed these mice with *Vgat-Cre* mice to introduce interneuron-specific TPP1 deficiency. We are currently exploring whether this impacts seizure generation through longitudinal EEG recording. We will report the outcome of these studies to determine whether interneuron network dysfunction is sufficient to trigger the spontaneous seizures and other neuropathological changes that characterize CLN2 disease.

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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.; Regenxbio Inc.

**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.26/G5

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

**Support:** NIH Grant AG060731
MSU - Department of Translational Neuroscience

**Title:** Development of a novel translational rat model of Dementia with Lewy bodies

**Authors: *M. HORE**, C. J. KEMP, J. R. PATTERSON, J. W. HOWE, M. KUBIK, M. GIFANI, C. E. SORTWELL, S. E. COUNTS;
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**Abstract:** Dementia with Lewy Bodies (DLB) is the second most common neurodegenerative cause of dementia after Alzheimer's disease. Clinical features of DLB include variable attention and alertness, spontaneous parkinsonism, rapid eye movement sleep disorder, and recurrent visual hallucinations. DLB is characterized by: 1) aggregates of, alpha-synuclein (α-syn) Lewy bodies (LBs), amyloid-beta (A$\beta$;) peptides as plaques and, to a variable extent, hyperphosphorylated tau protein as neurofibrillary tangles (NFTs); 2) Nigrostriatal degeneration; and 3) DLB-relevant behavioral symptomatology. Aggregated co-occurring proteinopathies in DLB are particularly prominent in cortical (temporo-occipital) and limbic (entorhinal cortex, cingulate, hippocampus CA1) regions. Some characteristics of DLB such as LB and plaque co-pathologies have been replicated in rodent models. However, no rodent model has recapitulated the full spectrum of DLB. Thus, we are developing a novel DLB rat model by combining the transgenic (Tg) F344 rat model of Alzheimer's Disease (AD) with specifically targeted intracerebral injections of mouse α-syn preformed fibrils (PFFs). The TgF344-AD rat model expresses mutant human amyloid precursor protein and presenilin 1 genes resulting in age-dependent accumulation of plaques and NFTs, cortical and hippocampal neurodegeneration, and cognitive disturbances. Nigrostriatal α-syn PFF injections result in accumulation of pathological α-syn in cortical, limbic and nigrostriatal regions, followed by nigrostriatal degeneration and motor deficits. Total of 14 male F344 wildtype (WT) and AD Tg rats have received bilateral intranigral injections of α-syn PFFs or α-syn monomer (control) at 6 months of age, which will be followed by additional bilateral intrastriatal PFF and monomer injections at 10 months of age. Rats will be assessed for behavioral performance prior to euthanasia at 14 months of age. We hypothesize that PFF injected TgF344-AD rats will exhibit: 1) abundant LBs, plaques, and NFT co-pathologies with upregulation of neuroinflammatory markers in cortical and limbic brain areas; 2) significant nigrostriatal degeneration; and 3) behavioral impairments. Postmortem assessments will focus on the amygdala, entorhinal cortex, cingulate cortex, hippocampus,

striatum and substantia nigra to determine the impact of plaques + NFTs with and without LB co-pathology; glial reactivity; and neurodegeneration. A rodent model that integrates the entire repertoire of DLB co-pathologies and related behaviors will increase understanding of the proteinopathy in DLB and facilitate preclinical assessment of novel disease modifying therapies.

**Disclosures:** **M. Hore:** None. **C.J. Kemp:** None. **J.R. Patterson:** None. **J.W. Howe:** None. **M. Kubik:** None. **M. Gifani:** None. **C.E. Sortwell:** None. **S.E. Counts:** None.

**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.27/G7

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

**Support:** ADTP T32 2T32AG052354-06A1

**Title:** Expression of TMEM106B C-Terminal Fragment Drives Neurodegenerative Proteinopathy in Transgenic C. Elegans

**Authors: *R. RIORDAN**[1,5], A. SAXTON[5,2], P. MCMILLAN[5], C. LATIMER[3], D. C. KEENE[3], N. LIACHKO[5,4,3,2], B. KRAEMER[5,4,3,2];
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**Abstract:** Neurodegenerative diseases such as Alzheimer’s Disease (AD) and frontotemporal lobar degeneration (FTLD), commonly involve aging related protein aggregation of specific proteins, which leads to neuronal impairment or death. In many cases of AD and AD related dementia (ADRD), one or multiple aggregating proteins form inclusions driving neurodegenerative disease. Diseases driven by dysfunctional aggregated proteins are called proteinopathies and exhibit aggregates of $A\beta_{1\text{-}42}$, FUS, Synuclein, tau, TDP-43, and/or UBQLN2. Understanding the mechanisms through which protein aggregation drives neurodegeneration as well as the interplay between distinct pathological proteins is vital for developing and improving therapeutic interventions for such disease. Genetic variation of lysosomal protein, transmembrane protein 106B (TMEM106B) is known as a risk factor for a diverse range of neurodegenerative disorders, especially FTLD with progranulin (GRN) haplo-insufficiency, though the mechanisms involved are not yet understood. Through advances in cryo-electron microscopy (cryo-EM), aggregates of the C-Terminal domain of TMEM106B (TMEM CT) were discovered to make up previously unidentifiable protein aggregates in the brains of human FTLD, AD, progressive supranuclear palsy (PSP), and dementia with Lewy Bodies (DLB) patients. While it is currently unknown what role TMEM CT aggregation plays in neuronal loss, its presence across a variety of neurodegenerative diseases indicates involvement in multi-proteinopathy driven neurodegeneration. To determine the TMEM CT aggregation propensity

and neurodegenerative potential, we characterized a novel C. *elegans* model expressing the TMEM CT fragment constituting the fibrillar core in FTLD cases. We found that C. *elegans* pan-neuronal expression of TMEM CT causes neuronal dysfunction as evidenced by behavioral analysis. Behavioral dysfunction was accompanied by neurodegeneration as illustrated by loss of GABAergic neurons. To investigate the mechanisms driving TMEM106B proteinopathy, we aimed to explore the impact of GRN loss on the neurodegenerative effect of TMEM CT expression. To this end, we generated TMEM CT expressing C. *elegans* with either full or partial loss of progranulin-1 (PGRN), the C. *elegans* equivalent of human GRN. Neither full nor partial loss of PGRN altered the motor phenotype of our TMEM CT model, indicating the role of PGRN may be too far upstream in pathology to observe in our model. Taken together, our data suggest expression of TMEM CT in C. *elegans* neurons provides a useful model for the functional characterization of TMEM106B proteinopathy in neurodegenerative disease.

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**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.28/G8

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

**Support:** Dr. Willmar Schwabe GmbH & Co. KG

**Title:** Mitochondrial effects of plant extracts in pathological aging and Alzheimer´s disease

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**Abstract:** Mitochondrial dysfunction is one of the major pathologic hallmarks in aging and late onset Alzheimer's disease (LOAD). Several alterations in mitochondrial function are described such as reduced mitochondrial membrane potential (MMP), lower ATP levels and enhanced reactive oxygen species (ROS). These alterations are strongly related to a decreased effectivity of the respiratory chain (OXPHOS). In addition, the protein expression of several complexes of the OXPHOS including complex I is reduced in aging and LOAD. Previous data from our group showed, that complex I-derived ROS shift Amyloid precursor protein (APP) processing towards toxic Amyloid β (Aβ) generation, initiating this vicious cycle. Therefore, we analyzed whether plant extracts such as Ginkgo biloba or other potent antioxidant extracts affect mitochondrial dysfunction! First, to investigate protective effects of a selection of 48 defined plant extracts on

mitochondrial function, a screening was performed by measuring ATP levels (n=6) in SH-SY5Y Mock cells in physiological conditions. To evaluate basal effects, we used piracetam (metabolic enhancer) as positive control and rotenone (complex I inhibitor) as negative control. Our results allowed us to select extracts regarding their significant increase in ATP formation. 20 plant extracts proved to be very promising. Second, we investigated effects of these plant extracts on MMP and complex I activity (n=6). This suggests that they have beneficial effects on improving mitochondrial function. To analyze alterations in protein expression in future experiments, we already treated cells with extracts for 24 h during the screening process. In conclusion, we identified 10 highly interesting plant extracts with protective effects on mitochondrial function!

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**Poster**

**PSTR014. Dementias and Proteinopathies: Mechanisms and Pathology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR014.29/G9

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

**Support:** JSPS KAKENHI Grant Number 20K09876
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Takeda Science Foundation
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Tohoku University Center for Gender Equality Promotion (TUMUG) Support Project

**Title:** Elucidation of the regulatory mechanisms of neurite outgrowth of the trigeminal mesencephalic nucleus neurons by Wnt5a, released from mechanically stimulated rat periodontal ligament cells

**Authors: *K. TAKAHASHI**[1], T. YOSHIDA[2], T. NAKAMURA[1], M. WAKAMORI[1];
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**Abstract:** Although many cohort studies have shown an association between poor oral function and the development of dementia and cognitive decline, the molecular physiological mechanisms linking poor oral function and dementia are not clear. In Alzheimer's disease, neuronal cell death occurs in the locus coeruleus (LC) early in the dementia. Recently, it was reported that tooth extraction decreases the number of neurons in the locus coeruleus. When bite pressure is applied to the teeth, primary sensations are transmitted from the periodontal ligament (PDL) to the trigeminal ganglion (TG) and the trigeminal mesencephalic nucleus (Me5), and from the muscle

spindles of the masseter muscle to the Me5. Primary sensory neurons are usually located outside the brain (e.g., dorsal root ganglion, trigeminal ganglion, and ganglia of glossopharyngeal and vagus nerves). However, the Me5 is exceptionally located inside the brainstem, adjacent to the LC. Neurotrophic factors such as NGF and BDNF and axon guidance proteins including Wnt family are known to be involved in neurite outgrowth. The rPDL cells expressed *Ngf*, *Bdnf*, *Ntf4* and *Wnt5a*. Only *Wnt5a* in rPDL cells increases in a stimulation-period dependent manner, and enhances neurite outgrowth in trigeminal ganglion neurons (Takahashi, et al., 2022). We hypothesize that factors released from mechanically stimulated PDL cells similarly regulate survival and maintenance of the Me5 neurons.We established primary PDL cell lines derived from rat molar tooth. The rPDL cells were loaded with periodic mechanical stimulation (0.5 Hz, 15% elongation). The culture medium for the primary mouse Me5 neurons was replaced with the supernatant media of the rPDL cells with or without mechanical stimulation. The supernatant medium of the mechanically stimulated rPDL cells enhanced the neurite outgrowth and this effect was suppressed by anti-Wnt5a antibody. One month after tooth extraction, Wnt5a protein in Me5 was predominantly reduced compared with that of control mice ($p=0.016$, $n=4$, paired t-test) using ELISA. These results suggest that Wnt5a, produced by mechanically stimulated rPDL cells, regulates neurite outgrowth of Me5 neurons.

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**Poster**

**PSTR015. Alzheimer's Disease: Mechanisms and Cognition**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR015.01/G10

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

**Support:** Cognito Therapeutics, Inc.

**Title:** Resting state EEG metrics correlate with clinical and imaging markers in mild to moderate Alzheimer’s disease

**Authors: *O. E. ROWE**[1], Y. COOK[1], M. HAJOS[1,2], E. HEMPEL[1], K. G. SAIKALI[1], Z. MALCHANO[1], C. V. SESHAGIRI[1];
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**Abstract:** Sensory stimulation is an emerging therapeutic approach for the treatment of Alzheimer’s disease (AD). A recent study (Overture, NCT03556280) in mild-to-moderate AD participants showed that daily home-use of Cognito Therapeutics’ gamma frequency Sensory Stimulation System significantly slowed decline of function (AD Cooperative Study Activities of Daily Living (ADCS-ADL)), cognition (Mini Mental State Exam (MMSE)), and MRI whole brain volume. Separately, several groups have investigated the relationship between resting-state

EEG (rs-EEG) and severity of AD. As rs-EEG offers an accessible physiological measurement, we characterized the relationship between rs-EEG and key clinical markers at baseline from Overture, a randomized, sham-controlled, 6-month clinical trial. Rs-EEG parameters included 90-180s recording of eyes-open and eyes-closed via a 32- or 64-Channel Waveguard Cap (ANT Neuro). EEG data from 70 participants with mild-to-moderate AD were bandpass filtered, referenced to a common average, and divided into 2-second epochs with 1-second overlap via MATLAB. Power spectra (Welch's method) were computed for all epochs and all available channels plus occipital-specific channels. Automated artifact detection was used to reject individual epochs, and estimates of relative power were estimated as the median of retained epochs. In addition, alpha/theta ratio was computed, as others have associated this with AD. Each metric was averaged across 30 channels of a 10-20 montage to a single estimate for each metric. Resulting EEG estimates were correlated with MMSE, ADCS-ADL, and normalized whole brain volume, which consists of structural T1-weighted MRI processed by Biospective Inc. and normalized by intracranial volume. Some datasets were missing or excluded due to quality. As this was an exploratory analysis, corrections for multiple comparisons were not performed. Occipital alpha/theta ratio was the strongest correlate for normalized whole brain volume (occipital left (OL): r=0.47 p=0.0008 n=48, occipital right (OR): r=0.46 p=0.0008 n=49), relative occipital alpha power for ADCS-ADL (OL: r=0.32 p=0.0107 n=61, OR: r=0.32 p=0.0115 n=62), and for MMSE (OL: r=0.41 p=0.0011 n=61, OR: r=0.38 p=0.0024 n=62). These findings broadly align with other groups who have established a relationship between decreased alpha power and increased volumetric atrophy/decreased MMSE scores in AD. By investigating the relationship between rs-EEG and disease state, we aim to establish a foundation for evaluating the effects of Cognito Therapeutics' Sensory Stimulation System on disease state as reflected by rs-EEG.

**Disclosures:** **O.E. Rowe:** A. Employment/Salary (full or part-time); Cognito Therapeutics, Athinoula A. Martinos Center for Biomedical Imaging. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognito Therapeutics. **Y. Cook:** A. Employment/Salary (full or part-time); Cognito Therapeutics. **M. Hajos:** A. Employment/Salary (full or part-time); Cognito Therapeutics, Yale University School of Medicine. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognito Therapeutics. **E. Hempel:** A. Employment/Salary (full or part-time); Cognito Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognito Therapeutics. **K.G. Saikali:** A. Employment/Salary (full or part-time); Cognito Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognito Therapeutics. **Z. Malchano:** A. Employment/Salary (full or part-time); Cognito Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognito Therapeutics. **C.V. Seshagiri:** A. Employment/Salary (full or part-time); Cognito Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognito Therapeutics.

**Poster**

**PSTR015. Alzheimer's Disease: Mechanisms and Cognition**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR015.02/H1

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

**Title:** Proteomic changes in Alzheimer's Disease patients after gamma sensory stimulation

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**Abstract:** Preclinical transgenic mouse models of Alzheimer's disease (AD) have shown that non-invasive, visual and auditory gamma sensory stimulation diminishes AD-related pathologies. The Sensory Stimulation System is a home-use gamma sensory stimulation device developed by Cognito Therapeutics, Inc. (Cambridge, MA) to evoke steady state, EEG-confirmed, gamma oscillations in humans for the treatment of AD. In the FLICKER study (NCT03543878) ten, amyloid positive participants with MCI were recruited from the Emory Goizueta Alzheimer's Disease Research Center (ADRC) and received 4 or 8 weeks of daily, one-hour gamma sensory stimulation. Cerebrospinal fluid (CSF) was collected at baseline, 4- and 8-week follow-up time points. Unbiased proteomic analysis of CSF samples was conducted to characterize underlying mechanism of action and assess effects of treatment using sensory stimulation. Unbiased proteomic quantification and analysis was conducted (Emtherapro, Atlanta, GA) using tandem-mass tag mass spectrometry (TMT-MS) of CSF collected from FLICKER participants. CSF proteome of FLICKER participants were mapped to the brain-derived co-expression modules to characterize underlying mechanism of action at a molecular level and, to assess effect of treatment on participants (Johnson et. al., 2022). A total of 2,785 CSF proteins were detected across all CSF samples. Differential expression analysis of proteins from baseline (N=5) vs. FLICKER treatment (N=5, 8 weeks) revealed 110 proteins that met the significance threshold of $p<0.05$ with 60 proteins upregulated and 50 proteins downregulated as result of treatment. Treatment had a significant impact on CSF proteins linked to AD biologies represented by brain modules related to Complement/acute phase (M26), Synapse/neuron (M1), Oligo/myelination (M3), Post synaptic density (M5), and Neurotransmitter regulation (M36). Ongoing analysis is focused on mapping CSF proteins to cell-type specificity to identify cells involved in gamma sensory stimulation. These results show human biomarker support demonstrating the broad mechanism of gamma sensory stimulation on white matter changes, synaptic regulation, glial function, and immunological responses.

**Disclosures:** **M. Shpokayte:** A. Employment/Salary (full or part-time); Cognito Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognito Therapeutics. **K. Pandey:** A. Employment/Salary (full or part-time); Emtherapro. **A.C. Singer:** F. Consulting Fees (e.g., advisory boards); Cognito Therapeutics. **D. Doung:** A. Employment/Salary (full or part-time); Emtherapro. **J. Lah:** None. **A.I. Levey:** F. Consulting Fees (e.g., advisory boards); Cognito Therapeutics. **N. Seyfriend:** None. **Z. Malchano:** A. Employment/Salary (full or part-time);

Cognito Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognito Therapeutics. **M. Hajós:** A. Employment/Salary (full or part-time); Cognito Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognito Therapeutics.

**Poster**

**PSTR015. Alzheimer's Disease: Mechanisms and Cognition**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR015.03/H2

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

**Title:** Understanding the mechanisms of synaptic vesicle glycoprotein 2A changes in Alzheimer’s disease

**Authors: *D. KING**[1], Y. YIN[1], K. HOLT[2], S. GLADSTEIN[4], W. HORTON[5], A. BEVIS[5], D. SMITH[6], H. ZETTERBERG[7], S. FINNEMA[8], T. L. SPIRES-JONES[3];
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**Abstract:** Background: Synaptic vesicle glycoprotein 2A (SV2A) is a transmembrane synaptic vesicle protein that regulates vesicle exocytosis and neurotransmitter release. Positron emission tomography (PET) studies reveal that the levels of SV2A are decreased in the brains of patients with Alzheimer’s disease (AD) and other brain disorders. Whether changes in SV2A PET signal are caused by a loss of synapses or a loss of SV2A protein is unclear and an impediment to developing novel treatments for neurodegenerative diseases. The goal of this study is to determine the biological underpinnings of reduced SV2A signal in individuals with AD. Method: We examined post-mortem brain samples from the entorhinal cortex (EC) and cerebellum (CBM) in AD patients and age- and sex-matched controls without neurological conditions (EC n=19 AD, 15 controls; CBM n=11 AD, 12 controls). We explored differences in synaptic density and synaptic ultrastructure using array tomography and electron microscopy, and analyzed data using linear mixed-effects models (with post-hoc Tukey comparisons) and Spearman correlations. Results: SV2A puncta density measured with array tomography in both brain regions strongly correlates with synaptophysin puncta density, the gold standard marker for synapse density in post-mortem brain tissue ($p=0.87$EC, $p=0.72$ CBM, $p<0.001$ both regions). We observed regional differences in SV2A densities between CBM and EC and slightly higher SV2A puncta density in AD CBM ($p=0.006$) cases compared to controls. There were no difference in the proportion of synaptophysin puncta labelled with SV2A in AD vs control ($p=0.39$). Electron microscopy revealed immunogold labelled SV2A protein localized

specifically to presynaptic vesicles and no difference in the number of immuno-gold labelled SV2A particles per synapse (p=0.53). Conclusion: Our data indicate that the loss of SV2A PET signal reported in vivo in patients with AD is likely caused by a loss of synapses and not the loss of SV2A protein within remaining synapses. These findings indicate that changes in SV2A PET signal are due to synaptic loss and that strategies for reversing synaptic loss or associated neuropathophysiological effects may be important to the treatment of AD and other synaptopathies. This work is part of the SV2A PET Project, a program of the FNIH Biomarker Consortium.

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**Poster**

**PSTR015. Alzheimer's Disease: Mechanisms and Cognition**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR015.04/H3

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

**Support:** Hevolution/AFAR
R01AG068293

**Title:** Investigating the role of $p19^{INK4d}$ in neuronal senescence

**Authors: *H. R. HUDSON**[1], T. ORR[2], M. ORR[3];
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**Abstract: Background:** Cellular senescence is a stress response characterized by resistance to apoptosis, cell cycle arrest, and the release of senescence-associated secretory protein (SASP) implicated in Alzheimer's disease and related dementias (ADRD). Previous studies in our laboratory have identified an upregulation of *CDKN2D/* $p19^{INK4d}$ expression in neuronal senescent cells in postmortem human brains with various levels of AD neuropathology. We hypothesized that overexpressing *Cdkn2d* would induce senescence in mouse neurons i*n vivo.* **Methods:** Experimental *Cdkn2d*-GFP, or control GFP gene expression were delivered using adeno-associated virus 9 (AAV9) with the neuron specific human Synapsin I (hSyn1) promoter. Precise delivery of 0.5µl of $10^{13}$ IU virus into four neuronal populations per mouse, bilateral hippocampal CA1 and cortical layer 5 neurons was accomplished with the assistance of a stereotaxic robot. Male and female wild type, human tau transgenic and mouse tau knockout mice were used (12-13 months-old, n=10-14 per group). Mice were euthanized at either two weeks or eight weeks post-surgery to determine the short- and long-term effects of *Cdkn2d* expression. GeoMx digital spatial profiler was utilized to quantify protein expression between *Cdkn2d* infected and uninfected neighboring neurons along with protein expression across

genotypes and injection groups. **Results:** Histological analyses confirmed $p19^{INK4d}$ protein expression in AAV9-GFP infected cells. GeoMx DSP analyses were performed on the hippocampus, cortex, and thalamus comparing the infected and uninfected neurons within each region. The results revealed a protein expression pattern consistent with senescence (*i.e.*, resistance to apoptosis), in *Cdkn2d*-expressing neurons of the hippocampus and cortex. In contrast, proteins associated with apoptosis were higher in the thalamus compared to the cortex and hippocampus. Analyzing these same regions across tau genotypes has revealed interactions between tau and effects of $p19^{INK4d}$ expression. **Conclusion:** The data indicates that AAV9-hSyn1-*Cdkn2d*-GFP is an appropriate method to increase $p19^{INK4d}$ expression in mouse neurons *in vivo*. Over-expressing $p19^{INK4d}$ caused neurons to acquire a protein expression signature consistent with senescence. Further studies are needed to continue exploring the effects of *Cdkn2d* on neuronal senescence, and how tau protein may influence this stress response.

**Disclosures: H.R. Hudson:** None. **T. Orr:** None. **M. Orr:** None.

**Poster**

**PSTR015. Alzheimer's Disease: Mechanisms and Cognition**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR015.05/H4

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

**Support:** NIH Grant R01-AG052419
NIH Grant P30-AG21332
NIH Grant UL1-TR00120

**Title:** Beta amyloid accumulation predicts grocery shopping performance in older adults without cognitive impairment

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**Abstract:** Early identification of Alzheimer’s disease (AD) risk is crucial to slow progression. However, quantifying beta amyloid (Aβ) accumulation through imaging is expensive. Aβ accumulation may subtly impact the recruitment and coordination of different cognitive functions needed to perform a complex task like grocery shopping. The purpose of this study was to identify if performance of a grocery shopping task could differentiate older adults (OA) at high risk of developing AD (Aβ+), OA at low risk of developing AD (Aβ-), and young adults (YA), and if Aβ accumulation could predict grocery shopping performance in OA. **METHODS:** Twenty-two Aβ+ without cognitive impairment (79±5 years old, 9 females), 33 Aβ- without

cognitive impairment (78±5 years old, 15 females), and 29 YA (31±3 years old, 18 females) participated. Participants performed four grocery shopping trials, with the best and worst performances analyzed. The elapsed time to select the prespecified grocery item, the number of fixations on the grocery note naming the prespecified grocery item, and the percentage of time fixating on any grocery item, on grocery items on the correct shelf, and on grocery items from the correct brand were recorded. Linear mixed effect ANOVAs compared outcome measures by group (Aβ+, Aβ-, and YA). Additional linear mixed effects regressions estimated the effect of Aβ accumulation (continuous variable) on outcome measures in the OA. **RESULTS:** There was no difference between Aβ- and Aβ+ in the time to select a grocery item ($p>0.05$). Aβ+ looked at the grocery note more often than did YA ($p=0.036$), and a higher Aβ predicted a greater number of glances at the grocery note in OA ($p=0.035$). YA and Aβ- fixated on grocery items for a larger percentage of time during their worst relative to their best performances (YA: $p<0.001$; Aβ-: $p<0.001$). Continuous Aβ values did not predict percentage of time fixating on grocery items in OA ($p>0.05$). Aβ+ and YA fixated on the correct shelf for a smaller percentage of time (YA: $p=0.002$; Aβ+: $p<0.001$) during their worst trials relative to their best trials, and a higher Aβ predicted that an OA would look at the correct shelf ($p=0.049$) and the correct brand ($p=0.037$) for a smaller percentage of time during their worst performance. **CONCLUSIONS:** Aβ+ individuals and individuals with higher Aβ accumulation exhibited less efficient grocery item search strategies. This was evident through more glances at the grocery note and less time fixating on the correct shelf or brand, despite no difference in time to select an item between groups. Less efficient search strategies may be the result of preclinical deficits in working memory or executive function.

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**Poster**

**PSTR015. Alzheimer's Disease: Mechanisms and Cognition**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR015.06/H5

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

**Support:** HI20C0206
2017R1D1A1B05028221

**Title:** Amlexanox, a phosphodiesterase inhibitor, relieves lysosomal dysfunction via increasing cAMP levels in cultured cortical astrocytes, and ameliorates pathology and cognition in 5X FAD mice

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**Abstract:** Amlexanox (Aphthasol) is an anti-inflammatory drug used to topically treat apthous ulcers. While its mechanism of action is not clear, it may reduce histamine and leukotriene release from inflammatory cells. After we found that PDE inhibitors potentiates lysosomal functions via increasing cAMP levels, we high-throughput screened an FDA-approved drug library for possible PDE inhibitors. Amlexanox was found to be one of the candidates, and we examined whether it has a lysosomal-potentiating effect in cultured cortical astrocytes. In addition, we tested whether amlexanox has an beneficial effects in 5X FAD mice model. In test tube experiments, amlexanox inhibited all forms of PDEs with similar IC50s, indicating that it is rather a broad-spectrum PDE inhibitor. In cultured cortical astrocytes, addition of amlexanox (10 μM) increased cAMP levels in a concentration-dependent manner. Concurrently western blots for phosphorylated forms of protein kinase A substrates showed that amlexanox increased PKA activity; addition of PKA inhibitor blocked the amlexanox effect. When cultured cortical astrocytes were treated with bafilomycin A1, a selective and potent inhibitor of vATPase, the lysosomal proton pump, shifted lysosomal pH to the alkaline direction as shown by LysoSensor fluorescence, and blocked autophagy flux as indicated by an increase in p62 levels. Addition of amlexanox restored the lysosomal acidity almost to the control levels, and normalized autophagy flux as well. These effects were reversed by the addition of PKA inhibitor H-89. Next, we examined whether amlexanox would have beneficial effects against Aβ-induced lysosomal dysfunction. Aβ alone was sufficient in altering lysosomal pH and increasing p62 levels. Again amlexanox reversed both effects by Aβ. Finally, we treated 5X FAD mice with 2.5 mg/kg injections of amlexanox for 3 months (from 3 - 6 month). In water maze tests, amlexanox-treated mice performed significantly better. Postmortem brain examinations showed that amlexanox treatment reduced Aβ and p-Tau deposition in cortex and hippocampus. Present study showed that amlexanox re-normalizes lysosomal functions in cultured cortical astrocytes, and has beneficial effects in a mouse model of AD. Since amlexanox is being used in human asthma and allergy patients, its potential side effects may not be great and thus clinical trials may need less time than novel chemicals.

**Disclosures: H. Kim:** None. **Y. Yoon:** None. **J. Koh:** None.

**Poster**

**PSTR015. Alzheimer's Disease: Mechanisms and Cognition**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR015.07/H6

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

**Support:** DVR Grant R01AG058162

**Title:** Dynamic vasomotor reactivity, white matter hyperintensity volume, and cognitive performance in cognitively impaired versus unimpaired older adults

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**Abstract:** The established relationship between cerebrovascular dysregulation and cognitive impairment led to a search for model-based "physiomarkers" of cerebral hemodynamics for improved non-invasive, early detection of mild cognitive impairment (MCI) and Alzheimer's Disease (AD). Dynamic vasomotor reactivity (DVR) quantifies the cerebral flow response to end-tidal $CO_2$ changes and is extracted from dynamic modeling of time-series data collected at the middle cerebral arteries (MCA) by a transcranial doppler (TCD) probe. DVR is lower in people with cognitive impairment compared to cognitively normal (CN) controls. Here we investigate whether the relationship between DVR and white matter hyperintensity (WMH) volume and cognitive testing differs by cognitive group. Our study yields important information about interpreting relative DVR values. We scanned 55 older adults (31 CN, 11 MCI, 13 mild dementia with clinical diagnosis of AD; age 74 ± 7.5; Siemens 3T MRI) at the University of Southern California or University of Kansas Medical Center. Participants underwent the Uniform Data Set (UDS) Version 3 Neuropsychological Test Battery and TCD-derived DVR. WMHs were measured on FLAIR MRI (SPM's LGA toolbox). We selected tests evaluating DVR-relevant domains: category fluency (vegetables), Craft story - delayed recall, multilingual naming test (MINT) total score, and MoCA - delayed recall. All continuous measurements were z-scored. In separate multiple linear regression models (RStudio 4.2.2), we evaluated the interaction between cognitive diagnosis and DVR on 1) WMH volume and 2) neuropsychological test performance, covarying for age, sex, years of education, and *APOE*4 genotype, and for intracranial volume on the WMH analysis. Correcting for site did not affect the results. We used the false discovery rate method to correct for multiple comparisons. DVR was higher overall in CN versus MCI ($p$=0.0003, $z$=-3.58) and AD ($p$=0.008, $z$=-2.64) groups. Higher DVR was associated with lower WMH volume in CN and MCI groups, but higher WMH volume in AD (FDR $p$=0.04, $\beta$=0.65 ± 0.31). Higher DVR was associated with higher MINT test scores in the CN group, but lower scores in MCI and AD groups (FDR $p$=0.02, $\beta$=-0.70 ± 0.23). We performed secondary analyses using amyloid-beta (Aβ) positivity as a covariate and then as an interaction term (n=40, Aβ+=19). Positivity was established with a cutoff of 1.08 for florbetaben PET global standardized uptake value ratio (SUVR). Aβ analyses did not modify the results, suggesting that in people with AD, altered vascular reactivity may be related to some other physiological stressor concurrently injuring the brain and driving worse cognitive performance.

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**Poster**

**PSTR015. Alzheimer's Disease: Mechanisms and Cognition**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR015.08/H7

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

**Support:** NIH Grant R01-AG052419
NIH Grant P30-AG21332
NIH Grant UL1-TR00120

**Title:** Rate of improvement while learning novel cognitive tasks as a potential identifier of preclinical Alzheimer's disease

**Authors: *L. HETRICK**[1], H. CHEN[3], L. A. ZUKOWSKI[2];
[2]Dept. of Physical Therapy, [1]High Point Univ., High Point, NC; [3]Dept. of Biostatistics and Data Sci., Wake Forest Univ. Sch. of Med., Winston-Salem, NC

**Abstract:** Cognitive declines associated with preclinical Alzheimer's disease (AD) overlap with typical age-related declines in cognition in healthy older adults (OA). Distinct tests of executive function and processing speed are not sensitive enough to differentiate between those with preclinical AD (e.g., beta amyloid (Aβ) accumulation) and typical age-related declines, but the rate of improvement (ROI) while learning new tasks that incorporate these cognitive functions may be more sensitive. The purpose of this study was to determine how age group, amount of practice, demographics, and performance on neuropsychological tests predict ROI during two novel cognitive tasks, and if Aβ accumulation impacts ROI in OA. **METHODS:** Fifty-five OA (78±5 years of age, 24 females) and 28 young adults (31±3 years of age, 17 females) participated. Aβ accumulation was assessed in OA. Participants completed neuropsychological tests, including the Comprehensive Trail Making Test (CTMT), Digit Symbol Substitution Test (DSST), Coding subtest, and Auditory Verbal Learning Test (AVLT). Demographic data, including gender and years of education, were collected. Participants learned two novel cognitive tasks: the stop-go normal task (SGNT), a test of processing speed, and the stop-go reverse task (SGRT), a test of executive function. ROI was analyzed as the percent change in cognitive performance from the first to second practice and from the first to third practice trials using a linear mixed effect model for the SGNT and SGRT. The basic model included age group, the two ROI values, and the interaction between age group and ROI, with subsequent models adjusting for demographic and neuropsychological test covariates. The second basic model mimicked the previous model but included Aβ accumulation, in lieu of age group. **RESULTS:** More practice resulted in a greater ROI for the SGNT ($p=0.001$) and SGRT ($p<0.001$). Age group, years of education, and gender did not impact ROI for either task (all $p>0.05$). None of the neuropsychological tests predicted ROI for the SGNT (all $p>0.05$). For the SGRT, better CTMT Total Composite Index ($p=0.003$), CTMT Inhibitory Control Index ($p=0.003$), CTMT Set Shifting Index ($p=0.01$), DSST ($p=0.04$), and Coding ($p=0.02$) performances predicted a smaller ROI; however, better performance on the AVLT predicted greater ROI ($p=0.04$). There was a non-significant trend of more Aβ accumulation resulting in a smaller ROI for both tasks ($p>0.05$). **CONCLUSIONS:** Executive function and processing speed of participants impacted ROI on the SGRT, with no difference between OA and YA. A larger sample size is needed to explore the trend of more Aβ accumulation in OA resulting in a smaller ROI.

**Disclosures:** **L. Hetrick:** None. **H. Chen:** None. **L.A. Zukowski:** None.

**Poster**

**PSTR015. Alzheimer's Disease: Mechanisms and Cognition**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR015.09/H8

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

**Title:** Characterization of a transgenic mouse model of tauopathy using quantitative EEG: Do tau-induced deficits lead to disrupted EEG spectra in brain structures ?

**Authors: *H. MONCHAL**[1], F. S. MENNITI[2], A. EVRARD[1], B. MANDÉ-NIEDERGANG[1], C. ROUCARD[1], Y. ROCHE[1], K. DUNTON[2];
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**Abstract:** Alzheimer’s disease (AD), the most common form of dementia, is associated with two pathological hallmarks: parenchymal beta amyloid deposition and intraneuronal neurofibrillary tangles formed from hyperphosphorylated tau. However, lack of understanding of how these primary pathologies result in cognitive deficits remains a hurdle to the development of meaningful therapeutics. To investigate a translatable model related to tau pathology, we undertook a study of changes in electroencephalography (EEG) characteristics with age in the P301L tauopathy mouse model. P301L mice overexpress the 4R/2N isoform of human tau under control of the CaMKIIα promoter on a C57BL/6 background. In this experiment, C57BL/6 will be used as controls and their EEG profile will be compared to the transgenic P301L in order to evidence a potential EEG biomarker related to the P301L mutation, or the lack thereof. In P301L mice and WT controls, monopolar electrodes were implanted bilaterally over the frontal cortex and over parietal cortex on one side. A depth electrode was also implanted in the hippocampus, with a reference electrode over the cerebellum. Animals were recorded for two hours once a month, beginning at 4 months of age. A Fast Fourier Transform (FFT) was performed on EEG signal from each electrode for frequencies ranging from 1 to 140Hz. In P301L mice up to 9 months of age, we observed a decrease of power in all classical frequency bands (from Delta to Epsilon) in the hippocampus as compared to WT. There was a persistent trend for an increase in high Delta in frontal cortex, and for a decrease in Theta in parietal cortex. Interestingly, this general pattern of change was evident from 4 months of age, the earliest time point recorded and evidenced little change out to 9 months of age. This study highlights the utility of EEG to identify subtle and persistent changes in brain function in response to AD-relevant tau pathology. Further characterization of the model, including study of the potential pharmaco-sensitivity of the phenotype to therapeutic intervention is ongoing.

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**Poster**

**PSTR015. Alzheimer's Disease: Mechanisms and Cognition**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR015.10/H9

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

**Title:** Comparison of cerebrospinal fluid biomarkers in people with mild cognitive impairment and Alzheimer's disease and the aged canine model of Alzheimer's disease

**Authors:** J. PRENDERVILLE[1], R. WINTERS[2], J. A. ARAUJO[3], ***C. DE RIVERA**[4];
[1]Transpharmation Ltd., Dublin, Ireland; [2]Transpharmation Ireland Ltd, Dublin, Ireland;
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**Abstract:** Mild cognitive impairment (MCI) is a disorder wherein an individual's cognitive decline is accelerated relative to their age group. MCI can progress to dementias such as Alzheimer's disease (AD). Canine ageing is associated with cognitive decline that is linked to neuropathological changes paralleling human AD. This includes amyloid-beta (A-beta) deposition, dystrophic neurites, neuronal loss, neuroinflammation, microgliosis and astrogliosis. The current study assessed cerebrospinal fluid (CSF) biomarkers of AD progression, neuroinflammation and neuronal cell damage in people with (Pw) MCI, PwAD and the aged canine model of AD. CSF from PwMCI, PwAD and age matched controls (n=15 per group) were obtained from a biobank. CSF was collected from three groups of beagles (n=13-15 per group): young (under 6 years), middle-aged (between 6 and 10 years) and aged (over 10 years). Protein biomarkers were analysed using the MESO QuickPlex SQ platform (Meso Scale Discovery). The A-beta peptide panel included A-beta38, A-beta40 and A-beta42. The cytokines interleukin (IL) -2, IL-6, IL-8 and tumor necrosis (TNF)-alpha were quantified. Neurofilament light chain (NfL) was also investigated. Data were analysed by one-way ANOVA or Kruskal-Wallis.In PwMCI and PwAD the A-beta42 / A-beta40 ratio was significantly decreased compared to age matched controls ($p<0.001$). The A-beta42 / A-beta40 ratio was significantly decreased in middle aged ($p<0.01$) and aged ($p<0.001$) dogs compared to young. In PwAD a significant increase in IL-6 ($p<0.05$) and IL-8 ($p<0.01$) was observed compared to age matched controls. In aged dogs a significant increase in IL-6 ($p<0.01$) and IL-8 ($p<0.01$) was seen compared to the young group. NfL was significantly increased in both middle aged ($p<0.01$) and aged ($p<0.001$) dogs compared to young.Recent therapeutic advances in the AD field have increased the need for translational models of disease progression that mimic the behavioural and neuropathological features of sporadic AD. Canine ageing is associated with cognitive impairment and pathophysiological changes in the brain that show similarities to AD. In this study, we report a comparable CSF protein biomarker profile in PwAD and the aged canine model of AD. A-beta CSF levels in aged dogs are altered in line with what is observed in PwMCI and PwAD. The inflammatory profile in aged dogs is comparable to that observed in PwAD. NfL, a marker of axonal damage in CSF associated with neurodegenerative disease, is increased during canine ageing. These data suggest the aged dog as an effective and translational model of AD.

**Disclosures:** **J. Prenderville:** A. Employment/Salary (full or part-time); Transpharmation Ireland Ltd. **R. Winters:** A. Employment/Salary (full or part-time); Transpharmation Ireland Ltd. **J.A. Araujo:** A. Employment/Salary (full or part-time); Transpharmation Canada Ltd. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); InterVivo Solutions Inc. **C. de Rivera:** A. Employment/Salary (full or part-time); Transpharmation Canada Ltd. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); InterVivo Solutions Inc.

**Poster**

**PSTR015. Alzheimer's Disease: Mechanisms and Cognition**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR015.11/H10

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

**Support:** KGM4562323
KFW0512311

**Title:** Increases of TREM2 and pTau181 level in cerebrospinal fluid in naturally aging monkeys

**Authors:** ***S.-W. LEE**[1,2], M. KIM[1,3], J. SEO[1], K. KIM[1,4], Y. JUNG[1,5], J. PARK[1], Y. LEE[1]; [1]Korea Res. Inst. of Biosci. and Biotech., Cheongju-si, Korea, Republic of; [2]Biotech. and Bioinformatics, Korea Univ., Sejong-si, Korea, Republic of; [3]Korea Advanced Inst. of Sci. and Technol., Daejeon-si, Korea, Republic of; [4]Kyungpook Natl. Univ., Daegu, Korea, Republic of; [5]Seoul Natl. Univ., Seoul, Korea, Republic of

**Abstract:** Many researchers have tried to finding and analyzing persistently Alzheimer’s disease (AD) biomarker in biofluid likes cerebrospinal fluid (CSF) and blood. In our study, we collected CSF and blood 15 cynomolgus monkeys of different age, and analyzed AD biomarker. We shared 3 cynomolgus monkey groups with old group (16-20 years old), middle group (12 years old), and young group (6 years old) according to their age. For using ELISA, we collected blood sample through lateral saphenous vein, and CSF sample by using cisterna magna (CM) route. We quantified A**β**-40, A**β**-42, neurofilament light chain (NFL), glial fibrillary acidic protein (GFAP) level in plasma, but the results were not significantly changes between three groups. We quantified A**β**-40, A**β**-42, p-Tau(T181), t-Tau, ApoE4, FABP3, Ferritin, TREM2 in CSF, and we found that pTau(T181) and TREM2 level were increased in two cynomolgus monkeys of old group. These results corresponded with other research that AD patients had level of p-tau(T181) and TREM2 higher than health group in CSF. In this study, we verified for increasing AD biomarker level in CSF of several aged cynomolgus monkeys. These findings are very useful references for analyzing AD pathology in old cynomolgus monkey.

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**Poster**

**PSTR015. Alzheimer's Disease: Mechanisms and Cognition**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR015.12/I1

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

**Support:** NRF-2022R1A2C1011996
NRF-2022K1A3A1A20015190
NRF-2022K2A9A1A01098131
22RB1130

**Title:** Selective serotonin reuptake inhibitors attenuate the cognitive deficits in the 5xFAD Alzheimer’s disease model mice.

**Authors: *H. CHOI**[1,2,3], S. AHN[1,2,3], S. YU[1,2,3], C. JEONG[1,2,3], Y. PARK[1,2,3], H. SEO[1,2,3]; [1]Hanyang Univ., Ansan-si, Korea, Republic of; [2]Ctr. for Bionano Intelligence Educ. and Res., Ansan-si, Korea, Republic of; [3]Inst. for Precision Therapeut., Ansan-si, Korea, Republic of

**Abstract:** Alzheimer’s disease (AD) is themost common type of dementia accompanied by cognitive impairment, memory loss,and emotional impact with behavioral changes. Although the major causes of ADhave not been fully understood, previous reports have demonstrated that theamyloid plaques, neurofibrillary tangles, neuroinflammatory responses areassociated with the progressive neurodegeneration in AD. Recently, there wereseveral reports for the anti-inflammatory effects and amyloid-beta clearanceeffects of selective serotonin reuptake inhibitors (SSRIs) in AD models. However,the underlying mechanisms of SSRIs in AD pathological environments are notclearly understood yet. In this study, we hypothesized that the chronicadministration of SSRIs improves the AD-like behaviors and recover the cellsfrom the neurotoxic environment in the AD models. We daily administeredsertraline (SER) and fluoxetine (FLX) into 5xFAD AD model mice for 4 weeks (10mg/kg, i.p.). After the injection of SER or FLX, we performed multiplebehavioral tests, including Morris water maze test, elevated plus maze test,and tail suspension test, to measure the effect of SSRIs on the cognitivefunction in AD model mice. 5xFAD mice showed 25% decrease of the time spent intarget quadrant in Morris water maze indicating cognitive deficit. SERincreased 9% of the time spent in the target quadrant and FLX increased 21.1 %of the time spent in the target quadrant compared to vehicle treatment group.FLX also significantly reduced the immobility time in tail suspension test,compared to the vehicle treatment group. We also found the significantlydecreased level of mRNA expression of inflammatory markers including IL-1 beta,IL-10 in AD model. These results suggest that chronic SSRI treatment attenuatesthe cognitive impairment and neuroinflammation in AD pathology.

**Disclosures:** **H. Choi:** None. **S. Ahn:** None. **S. Yu:** None. **C. Jeong:** None. **Y. Park:** None. **H. Seo:** None.

**Poster**

**PSTR016. Alpha-Synuclein: Models**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR016.01/I2

**Topic:** C.03. Parkinson's Disease

**Support:** CONAHCYT Scholarship No. 1028543
UDG through P3E-UDG-2021

**Title:** Complete Bee Venom controls the expression of alpha synuclein and tyrosine hydroxylase after intra-nigral lipopolysaccharide injection

**Authors: *A. K. LOMELI LEPE**[1], S. J. LÓPEZ PÉREZ[1], J. CASTAÑEDA-CABRAL[2], M. E. URENA-GUERRERO[3];
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**Abstract:** Alpha synuclein (α-syn) has a critical role in the development of synucleinopathies, being the presence of neuroinflammatory processes an important feature in the pathogenesis of this neurodegenerative diseases, resulting in microglial activation and upregulation of pro-inflammatory mediators, thus favoring the accumulation of α-syn. Recent studies have shown the anti-inflammatory and anti-immune effects of bee venom (BV) in various conditions that present with this background. In this sense, the aim of this work was to investigate if the BV could modulate α-syn accumulation after lipopolysaccharide induction. The effects of BV over the expression of α-syn and tyrosine hydroxylase (TH) after intranigral application of lipopolysaccharide (LPS) were measured in Male Wistar rats (200-250 g) that were injected with LPS (2.5 µg) (LPS group) or vehicle (SHAM group) in the substantia nigra (SN). From the fifth day after the animals were treated with 6 repeat doses of BV (1.5 mg/kg, by injection into acupuncture point ST36, every 48 h). The results were compared with Naïve and SHAM group. The expression of α-syn and TH proteins was measured by western-blot at 30 days-post-injection (DPI) of LPS or vehicle. We find that LPS induced an increase in monomeric α-syn in SN (*p=0.02 vs Naïve) and in STR (*p=0.02 vs Naïve) and the treatment with BV maintain the α-syn expression at levels of Naïve group in both SN and STR (*p=0.01 and p=0.04, respectively, vs LPS). Furthermore, the expression of TH was observed decreased after the LPS injection in SN (**p= 0.005 vs Naïve) and in STR (*p= 0.03 vs Naïve) in both ipsilateral areas, while BV treatment kept the TH expression at levels of Naïve group only in STR (*p= 0.04 vs LPS). These results indicates that BV counteract the LPS-induced α-syn overexpression, possibly controlling the neuroinflammatory mediators generated by the stimulus further preserving nigral dopaminergic neurons, highlighting the BV as a compound of interest in the field of study of pathogenesis, prevention and treatment of synucleinopathies.

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**Poster**

**PSTR016. Alpha-Synuclein: Models**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR016.02/I3

**Topic:** C.03. Parkinson's Disease

**Title:** Uncovering the role of c-fos induction in the bidirectional relationship between depression/anxiety behaviors and alpha-synuclein propagation in Parkinson's disease

**Authors: *S.-J. KIM**[1], J.-B. KIM[1,2,3], H. NOH[1,2,3], H. GHAE[1], S. PARK[1,2,3];
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**Abstract:** Parkinson's disease (PD) is the most common neurodegenerative movement disorder and the debilitating neuropsychiatric symptoms such as depression and anxiety precede the onset of hallmark motor symptoms of PD. α-Syn propagation has been highlighted to link with the progression of PD. However, the relationship between a-syn propagation and non-motor symptoms of PD remains elusive. Here, we investigated that depression/anxiety-like behaviors (induced by chronic restrain stress) and α-SYN propagation (induced by α-SYN PFF injection into the brain) might trigger each other in the mouse model system. Here, we demonstrate that chronic restraint stress (CRS) substantially increased depression/anxiety-like behaviors deficits and aggravated α-synuclein pathology induced by α-syn PFF injection into the brain, and a-syn propagation also enhanced depression/anxiety-like behavior deficits induced by CRS, which was accompanied by c-fos induction and robust microglial activation in different brain regions, such as the cingulate cortex, amygdala, and entorhinal cortex. The administration of T5224, a selective inhibitor of c-Fos/activator protein-1, ameliorated both depression/anxiety-like behavior deficits and a-syn pathology induced by both CRS and a-syn injection. These results indicate that behavioral deficits related to nonmotor symptoms facilitate the formation of α-SYN pathology synergistically, and c-Fos may be a promising target for developing therapeutics for PD nonmotor symptoms and related α-synucleinopathies.

**Disclosures: S. Kim:** None. **J. Kim:** None. **H. Noh:** None. **H. Ghae:** None. **S. Park:** None.

**Poster**

**PSTR016. Alpha-Synuclein: Models**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR016.03/I4

**Topic:** C.03. Parkinson's Disease

**Support:** 2050-00009B

**Title:** Whole-brain 3D mapping and quantification of pathological α-Synuclein aggregate spreading and toxicity in a mouse model of early-stage Parkinson's disease

**Authors: *F. SØRENSEN**[1,5], Y. GALLERO-SALAS[1], A. HØJRUP RUNEGAARD THOMSEN[2], P. JENSEN[5], U. ROOSTALU[1], J. HECKSHER-SØRENSEN[3], H. BJÖRK HANSEN[3], C. GRAVERSEN SALINAS[4];
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**Abstract:** Progressive spreading of α-synuclein (α-Syn) aggregates in the brain plays a key role in the prodromal phase of Parkinson's disease (PD). While several preclinical models of synucleinopathies have been developed for studying the neurotoxicity of prion-like α-Syn aggregate spreading, they remain to be systematically explored with regards to early pathological events that could potentially be targeted to delay or ultimately prevent progression of PD. Using 3D whole-brain light sheet fluorescence microscopy (LSFM), the present study aimed to provide detailed spatiotemporal insight into the transmission of misfolded, pathological α-Syn in the α-Syn pre-formed fibril (PFF) mouse model of PD. 8-weeks old C57BL/6 male mice received two unilateral intrastriatal injections of mouse α-Syn PFFs (mPFFs, 5 µg per injection site). Mice were terminated at 1-, 4-, 8-, or 12-weeks post injection, and whole-brains were immunolabelled for α-Syn phosphorylated at serine-129 (pS129), cleared, and scanned using LSFM. Deep-learning computational analysis enabled fast 3D mapping and quantification of whole-brain pathological α-Syn architecture at cellular resolution. Our LSFM pipeline revealed distinct phases and morphological features of endogenous α-Syn aggregate spreading and toxicity in a neural circuit-dependent manner, notably in neuronal axons and soma co-labelled for pS129-αSyn and tyrosine hydroxylase (TH), indicating high vulnerability of midbrain dopaminergic neurons to the progressive burden of α-Syn aggregation. In conclusion, we report 3D whole-brain architectural signatures of early- and late-stage PD in an industry-standard α-Syn PFF mouse model of PD. Our LSFM-deep learning pipeline is instrumental for whole-brain mapping of potential neuroprotective drug effects in preclinical development for PD and other synucleinopathies.

**Disclosures:** **F. Sørensen:** A. Employment/Salary (full or part-time); Gubra. **Y. Gallero-Salas:** A. Employment/Salary (full or part-time); Gubra. **A. Højrup Runegaard Thomsen:** A. Employment/Salary (full or part-time); Gubra. **P. Jensen:** None. **U. Roostalu:** A. Employment/Salary (full or part-time); Gubra. **J. Hecksher-Sørensen:** A. Employment/Salary (full or part-time); Gubra. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gubra. **H. Björk Hansen:** A. Employment/Salary (full or part-time); Gubra. **C. Graversen Salinas:** A. Employment/Salary (full or part-time); Gubra.

**Poster**

**PSTR016. Alpha-Synuclein: Models**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR016.04/I5

**Topic:** C.03. Parkinson's Disease

**Support:** Work supported by #NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006) – (DN. 1553 11.10.2022)

**Title:** Electrophysiological characterization of L444P GBA mutation Parkinson phenotype

**Authors: *A. ANDOLFI**[1], D. DI LISA[1], G. URAS[2,3], S. GRASSELLI[1], S. L. DEL POZO[2], S. MARTINOIA[1], A. H. SCHAPIRA[2], L. PASTORINO[1];
[1]Univ. of Genoa, Genova, Italy; [2]Univ. Col. London, London, United Kingdom; [3]Univ. of Sassari, Sassari, Italy

**Abstract:** Parkinson's Disease (PD) is the most common neurodegenerative disease after Alzheimer's Disease, characterized by dopaminergic deprivation in the basal ganglia, and the symptomatic therapy used in PD currently focuses on dopamine replacement strategies (Schapira et al., 2017). Approximately 5-15% of PD patients have mutations in the GBA gene, establishing it as the most prominent genetic risk factor for PD in terms of numerical significance (Smith & Schapira, 2022). Thanks to the cellular reprogramming protocols, induced pluripotent-stem-cell (iPSC) revolutionized stem cell research providing access to a huge variety of human cell lines (Takahashi & Yamanaka, 2006), allowing to realize of both healthy and pathologic *in vitro* models (Park et al., 2008). Specifically, the human iPSC-derived neurons model of PD studied *in vitro* highlighted how PD is characterized by different neuronal morphology, connectivity, and electrophysiological activity (Ronchi et al., 2021). In the last decades, microelectrode arrays (MEAs) emerged as a promising technique to allow a non-invasive recording of the extracellular activity. MEAs are considered the leading platform in the field of brain-on a-chip for investigating neuronal functions and dysfunctions, neurotoxicity and drug screening. In this work, MEAs technology was used to characterize the spontaneous electrophysiological activity of both healthy and diseased dopaminergic neurons. In particular, the aim of this work was to investigate the impact of L444P GBA mutation on functional activity. Wild type and dopaminergic neurons carrying the L444P GBA mutation were generated from iPSCs from healthy and PD patients. Neurons derived from the two different phenotypes were co-cultured with primary astrocytes onto MEA devices. The preliminary functional characterization revealed distinct electrophysiological behaviors between the two phenotypes, particularly in terms of burst duration. L444P GBA mutation Parkinson phenotype exhibited a significantly lower value of burst durations, consistent with the results of Ronchi et al. (Ronchi et al., 2021).

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**Poster**

**PSTR016. Alpha-Synuclein: Models**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR016.05/I6

**Topic:** C.03. Parkinson's Disease

**Support:** NIH R15 NS121784

**Title:** Inhibition of SENP1 nuclear translocation ameliorates the damage from preformed fibrils of alpha-synuclein

**Authors: *D. K. VERMA**, K. OFORI, D. WHEELER, Y.-H. KIM;
Biol. Sci., Delaware State Univ., Dover, DE

**Abstract:** The accumulation and aggregation of α-synuclein are the hallmark of Parkinson's disease (PD), but the molecular mechanisms responsible for the pathology are not fully understood. Post-translational modifications (PTM) of α-synuclein regulate its functions and properties including degradation, interactions with other proteins, aggregation and degradation. Small Ubiquitin-like modifier (SUMO) is a highly dynamic PTM process involved in various nuclear and extranuclear processes, such as subcellular protein targeting, mitochondrial fission and synaptic plasticity. Although deconjugation (deSUMOylation) is known to be catalyzed by a family of cysteine proteases, SUMO-specific proteases (SENPs), the consequences of (de)SUMOylation are not fully elucidated. We have characterized that SENPs are involved in detaching SUMO1 from α-synuclein protein after **p**re**f**ormed **f**ibrils of α-synuclein (PFF) exposure, which provides insights of understanding the idiopathic mechanisms of PD. We found that the level of SENP1 protein was significantly higher than other SENP isoforms in PD models (*in vitro*, *in vivo* & human PD patients). SENP1 is enriched in nuclear foci that partially overlaps with promyelocytic leukemia (PML) nuclear bodies. In this study, we have generated two sets of double point mutants of the nuclear localizing sequences (NLS) of SENP1 gene and transfected them into the N27p cells. In stable cell lines with the overexpression of Wildtype (WT) or NLS Mutated (Mut 1 or 2) SENP1 genes, we found that mutant SENP1 overexpressing N27p cell lines showed significantly elevated cell viability and diminished cytotoxicity compared to WT-SENP1 overexpressing N27p cells against PFF toxicity. The levels of ROS and protein aggregates derived from PFF were also significantly reduced in NLS mutated SENP1 overexpressed N27 cells, compared to WT or vehicle overexpression. Taken together, our results strongly suggest that the inhibition of SENP1 nuclear translocation can be broadly applied to halt the pathology of diverse neurodegenerative diseases including PD, due to the prevention of oxidative stress and protein aggregation. The interactions of SENP1 with target proteins and genes in nucleus still need to be explored for understanding the SENP1-mediated neuropathology in PD models.

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**Poster**

**PSTR016. Alpha-Synuclein: Models**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR016.06/I7

**Topic:** C.03. Parkinson's Disease

**Title:** Effects of lentiviral shRNA-mediated targeting of selected genes on alpha-synuclein aggregation in cortical neurons

**Authors: *L. STRID ORRHULT**[1], E. RANNIKKO[2], A. VUORENPÄÄ[2], J. PIHL[1], P. KARILA[1], A. DOMANSKYI[2], I. MALIK[2];
[1]Cellectricon AB, Mölndal, Sweden; [2]Orion Corp., Turku, Finland

**Abstract:** Insoluble aggregates (Lewy bodies) consisting of the misfolded protein alpha-synuclein (αSyn) progressively accumulate in the nervous system of most Parkinson's disease (PD) patients. This process can affect multiple cellular functions, such as mitochondrial respiration, stress response, and autophagy/lysosomal pathways, eventually leading to neuronal death. In the current study, the aim was to identify 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, aimed for down-regulation of target, 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 as number of NeuN-positive neurons and area of MAP2-positive neurites. Lentiviral shRNA-mediated downregulation of some targets caused effects on neuronal survival. However, one week after PFF addition, targeting Zscan21 (a transcription factor regulating αSyn), Vps35 (retromer complex component affecting lysosomal function) and Fyn (a kinase regulating αSyn uptake) resulted in an increase, whereas targeting Ppp1r15a (a stress-induced protein phosphatase regulator), USP14 (a deubiquitinase affecting autophagy) and Bach1 (a transcriptional repressor regulating cellular redox homeostasis) resulted in a decrease in αSyn aggregation without effects on neuronal health. Two weeks after PFF addition, targeting Atp13a2 (a lysosomal ATPase), Fyn and Aimp2 (a known modulator of αSyn aggregation) increased, and targeting Ppp1r15a, Rhot1 (involved in mitochondrial homeostasis), Ttbk1 (regulates phosphorylation of Tau) and Bach1 decreased αSyn aggregation without effects on neuronal health. For some of the targets, the effect on αSyn aggregation was thus time dependent. We conclude that our in vitro model is useful for identification of targets involved in modulation of αSyn aggregation and for understanding the αSyn aggregation process over time. 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. **E. Rannikko:** A. Employment/Salary (full or part-time); Orion Corporation. **A. Vuorenpää:** A. Employment/Salary (full or part-time); Orion Corporation. **J. Pihl:** A. Employment/Salary (full

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**Poster**

**PSTR016. Alpha-Synuclein: Models**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR016.07/I8

**Topic:** C.03. Parkinson's Disease

**Support:** Mitacs fellowship

**Title:** Mood & motor disturbances in Parkinson's disease: A new α-synuclein-based mouse model

**Authors: *F. VAHID-ANSARI**;
Univ. of Ottawa, Ottawa, ON, Canada

**Abstract:** Mood and motor disturbances in Parkinson's disease: A new α-synuclein-based mouse model Authors*F. VAHID-ANSARI, P.R. ALBERT, SH HAYLEY; Neuroscience, Carleton University and University of Ottawa, Ottawa, ON, CADisclosuresF. Vahid-Ansari: None. P.R. Albert: None. SH Hayley: None.
Depression is a common non-motor symptom that often emerges early, during the prodromal phase, of Parkinson's disease (PD). Emerging evidence has associated such depressive pathology with the distribution of α-synuclein (α-syn; PD-neuropathological hallmark) in brainstem and limbic regions. Depression in PD is also linked to deficits in serotonergic (5-HT) functions before any clear degeneration of the dopamine (DA) system is evident. Accordingly, we developed a new α-syn based model of PD to examine the progression of non-motor and motor deficits associated with 5-HT and DA impairments. We performed unilateral *icv* infusion of wild type and A53T mutant α-syn preformed fibrils (PFF) in adult male C57/BL6 mice to evaluate the brain-wide direction of pathological α-syn spread and aggregation. To assess the behavioural changes forced swim, sucrose preference and open field tests were performed after ½, 1, 2, 3, and 4-months post-surgery. We found that the PFFs (particularly the A53T mutant form) induced signs of anxiety and depressive-like behaviors at multiple times up to 4-month post-surgery, whereas minimal motoric changes were observed. However, Digigate analyses did reveal significant gait difficulties at the 4-month time. Initial p-α-syn immunostaining showed signs of accumulation within the basolateral amygdala, hippocampal regions, nucleus accumbens and cortex at 1- and 4-months post-surgery. Ultra-resolution imaging approaches will be used to further characterize the nature of the α-syn aggregates. These preliminary results support the contention that α-syn might act as a common stimulus for both mood and motor pathology in PD.

**Disclosures: F. Vahid-Ansari:** None.

**Poster**

**PSTR016. Alpha-Synuclein: Models**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR016.08/J1

**Topic:** C.03. Parkinson's Disease

**Support:** NIH R21 NS123512

**Title:** Alpha-synuclein overexpression in the basal ganglia vocal nucleus, Area X, alters waveform patterns in a zebra finch model of Parkinsonian vocal deficits

**Authors: B. R. DOMINGUEZ**[1], G. HOLGUIN[2], R. BJORK[3], S. L. COWEN[4], *J. E. MILLER[5]; [1]Neurosci., [2]Psychology, [3]Neurosci, Grad. Interdisciplinary Program in Neurosci, [4]Psychology, Evelyn F. McKnight Brain Inst., [5]Neurosci & Speech, Lang and Hearing Sci, Neurology, GIDP in Neurosci, BIO5 Inst., Univ. of Arizona, Tucson, AZ

**Abstract:** Parkinson's disease (PD) is a neurodegenerative disorder characterized by severe limb motor dysfunction. PD is diagnosed clinically when limb motor function deteriorates, which coincides with substantial loss of dopaminergic neurons in the midbrain. Alpha-synuclein (a-syn), a synaptic protein encoded by the *SNCA* gene, forms toxic aggregates in cell bodies and synapses, which are thought to be a contributing factor in neuronal cell death. Notably, individuals with PD often present with vocal motor impairments, including changes in pitch, amplitude (loudness), and timing, prior to the onset of limb motor dysfunction. This highlights the importance of investigating the genes and neural circuitry involved in PD-related vocal deficits as early biomarkers for this disease. We use the zebra finch songbird model (*Taeniopygia guttata*) to study the role of a-syn in modulating early vocal impairments. We have shown that adeno-associated virus (AAV)-driven overexpression of human (h) a-syn in the basal ganglia song nucleus, Area X, results in PD-like song changes (reduced singing, monoloudness, shortened syllable duration) compared to AAV-GFP control finches. Therefore, our objective is to assess how a-syn overexpression alters neuronal firing patterns in Area X, within the cortico-basal ganglia-thalamo-cortico loop. We predict that a-syn aggregation in *hSNCA*-overexpressing finches will cause decreased firing activity in medium spiny neurons (MSNs), resulting in an increased firing rate in globus pallidus-like projection neurons, ultimately manifesting in a PD-like vocal phenotype. To test this hypothesis, we employed *in vivo* recordings of Area X neurons using fixed array electrodes in anesthetized finches to examine neuronal waveforms and firing patterns between AAV-*SNCA*, AAV-control, and surgically naive finches. Preliminary results indicate that putative MSNs show lower peak firing activity and greater after-hyperpolarization potentials in the AAV-*SNCA* group compared to AAV-control finches. On-going work includes immunohistochemistry to clarify time- and cell type dependent features of a-syn pathogenesis that map onto the initial PD-like song changes. These results will aid in the identification of neural activity networks that contribute to neuropathological changes in vocalization, in an early PD state, and therefore have the potential to facilitate development of more effective early interventions.

**Disclosures:** **B.R. Dominguez:** None. **G. Holguin:** None. **R. Bjork:** None. **S.L. Cowen:** None. **J.E. Miller:** None.

**Poster**

**PSTR016. Alpha-Synuclein: Models**

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**Program #/Poster #:** PSTR016.09/J2

**Topic:** C.03. Parkinson's Disease

**Support:** The design, study conduct, and financial support for this research were provided by AbbVie

**Title:** Broad proteomics analysis of seeding-induced aggregation of α-synuclein in M83 neurons reveals remodeling of proteostasis mechanisms that might contribute to Parkinson's disease pathogenesis

**Authors: *C. LUMPKIN**[1], B. RAVIKUMAR[2];
[1]Abbvie, Cambridge, MA; [2]AbbVie, Cambridge, MA

**Abstract:** Aggregation of misfolded α-synuclein (α-syn) is a key characteristic feature of Parkinson's disease (PD) and related synucleinopathies. The nature of these aggregates and their contribution to cellular dysfunction is still not clearly elucidated. We employed mass spectrometry-based total and phospho-proteomics to characterize the underlying molecular and biological changes due to α-syn aggregation using the M83 mouse primary neuronal model of PD. We identified gross changes in the proteome that coincided with the formation of large Lewy body-like α-syn aggregates in these neurons. We used protein-protein interaction (PPI)-based network analysis to identify key protein clusters modulating specific biological pathways that may be dysregulated and identified several mechanisms that regulate protein homeostasis (proteostasis). The observed changes in the proteome may include both homeostatic compensation and dysregulation due to α-syn aggregation and a greater understanding of both processes and their role in α-syn-related proteostasis may lead to improved therapeutic options for patients with PD and related disorders.

**Disclosures:** **C. Lumpkin:** A. Employment/Salary (full or part-time); AbbVie. **B. Ravikumar:** A. Employment/Salary (full or part-time); AbbVie.

**Poster**

**PSTR016. Alpha-Synuclein: Models**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR016.10/J3

**Topic:** C.03. Parkinson's Disease

**Title:** In vitro modeling of Parkinson's disease using human pluripotent stem cell-derived midbrain neuron and microglia co-culture with alpha-synuclein fibrils

**Authors:** N. LEBLANC[1], J. CHAN[1], ***C. MAK**[1], W. LUO[2], I. SHLAIFER[2], T. DURCAN[2], A. C. EAVES[1,3], S. A. LOUIS[1], E. KNOCK[1,4];
[1]STEMCELL Technologies Inc, Vancouver, BC, Canada; [2]The Neuro's Early Drug Discovery Unit (EDDU), McGill Univ., Montreal, QC, Canada; [3]Terry Fox Laboratory, BC Cancer, Vancouver, BC, Canada; [4]Dept. of Biology, Simon Fraser Univ., Vancouver, BC, Canada

**Abstract:** Parkinson's disease (PD) is characterized by dopaminergic neuron loss and alpha-synuclein inclusions but its underlying molecular mechanisms are still unclear. In this study, we aimed to reproduce early molecular and cellular phenotypes of PD by treating a human induced pluripotent stem cell (iPSC)-derived midbrain neuron and microglia co-culture system with exogenous alpha-synuclein fibrils. Human iPSC-derived neural progenitor cells generated using the STEMdiff™ Neural Induction kit monolayer protocol were plated into STEMdiff™ Midbrain Neuron Differentiation Medium. Midbrain neuronal precursors were passaged after one week into STEMdiff™ Midbrain Maturation Medium and cultured for an additional week before treatment with 600 nM of alpha-synuclein preformed fibrils (PFFs) from the wild type (WT) form or the A53T mutant (linked to familial PD). In separate experiments, we co-cultured the midbrain neurons with microglia generated using the STEMdiff™ Microglia system for 2 days. The co-culture was then incubated with 600 nM of WT or A53T alpha-synuclein PFFs. After 14 days of treatment, the cells were fixed and stained for phosphorylated alpha-synuclein at serine residue 129 (pS129), a pathological post-translational modification of the protein observed in sporadic and genetic forms of PD, as well as β-tubulin III (βIII-TUB), tyrosine hydroxylase (TH), and ionized calcium binding adaptor molecule 1 (Iba1) for microglia. After treatment with WT and A53T PFFs, the number of pS129+ midbrain neurons increased by 1.59 ± 0.60-fold and 5.15 ± 2.39-fold, respectively, while the number of TH+ cells decreased by 0.61 ± 0.16-fold for WT and 0.66 ± 0.09-fold for A53T PFFs (mean ± SD; data normalized to untreated control; n = 6 from 3 cell lines). The addition of A53T PFFs also resulted in a decreased number of βIII-TUB+ cells (467 cells) compared to the untreated control (1057 cells), while this decrease was not observed when the neurons were co-cultured with microglia (971 cells; mean of n = 2) . These results suggest that α-synuclein fibrils promote phosphorylated α-synuclein accumulation and reduce the number of TH+ and βIII-TUB+ cells, contributing to the development of PD. Co-culture with microglia may mitigate this effect, suggesting a potential protective role of microglia during early stages of PD. This in vitro model of PD using α-synuclein PFFs in a co-culture of iPSCs-derived midbrain neurons and microglia provides a valuable tool for studying the molecular mechanisms of disease initiation and progression.

**Disclosures:** **N. LeBlanc:** A. Employment/Salary (full or part-time); STEMCELL Technologies. **J. Chan:** A. Employment/Salary (full or part-time); STEMCELL Technologies. **C. Mak:** A. Employment/Salary (full or part-time); STEMCELL Technologies. **W. Luo:** None. **I. Shlaifer:** None. **T. Durcan:** None. **A.C. Eaves:** A. Employment/Salary (full or part-time); STEMCELL Technologies. **S.A. Louis:** A. Employment/Salary (full or part-time); STEMCELL Technologies. **E. Knock:** A. Employment/Salary (full or part-time); STEMCELL Technologies.

**Poster**

**PSTR016. Alpha-Synuclein: Models**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

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**Topic:** C.03. Parkinson's Disease

**Support:** ASAP
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MJFF
Parkinson's Foundation

**Title:** Impact of a-synuclein pathology on corticostriatal synapses in Parkinson's disease

**Authors: *H. CHALLA**, C. BRZOZOWSKI, N. GCWENSA, L. VOLPICELLI-DALEY; Univ. of Alabama at Birmingham, Birmingham, AL

**Abstract:** Parkinson's Disease (PD) is the most common neurodegenerative motor disorder, pathologically characterized by proteinaceous α-synuclein aggregates, collectively termed Lewy pathology. Normally, α-synuclein is highly expressed in the presynaptic terminals of excitatory neurons. Lewy pathology is found in a subset of cortical layer 5 neurons, which project to the striatum. However, little is known about how Lewy pathology affects corticostriatal synapses. The M2 cortex is the only cortical brain region in which neurodegeneration occurs in PD. 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 *in vivo* rodent models, we utilize the preformed fibril (PFF) model. PFFs are generated from recombinantly expressed monomeric α-synuclein and injected into mice brains to corrupt endogenously expressed α-synuclein to form insoluble aggregates. PFFs or control α-synuclein monomers were injected into the M2 cortex to study M2-specific inputs in the striatum. To study corticostriatal synapses, we developed an image acquisition and analysis pipeline by combining the high-resolution imaging technique Expansion Microscopy (ExM), and IMARIS software for synapse morphology analysis. M2-cortical PFF injections caused robust somal and neuritic pathology in layer 5 neurons of the M2 cortex and the neighboring primary motor and anterior cingulate cortex. We also found pathology in brain 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 ExM and synaptic loci analysis approach with IMARIS, we found a significant reduction in corticostriatal synaptic loci in the dorsal striatum of M2-PFF injected animals. Additional preliminary data indicate morphological changes to the volumes of cortical presynaptic terminals upon aggregate formation. Our results suggest that aggregated α-synuclein in the cortex affects the synaptic density and morphology of excitatory synapses in the striatum. These findings are consistent with human PD and non-human primate PD models showing excitatory synapse loss in the striatum. Furthermore, our data points to an important role of cortical Lewy Pathology on the functionality of corticostriatal synapses, and future studies will

elucidate the mechanisms of how abnormal α-synuclein accumulations disrupt corticostriatal synapses and how this contributes to symptoms of PD.

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**Poster**

**PSTR016. Alpha-Synuclein: Models**

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**Topic:** C.03. Parkinson's Disease

**Support:** The Borealis Foundation
CIHR Grant 109555

**Title:** Utilization of a DNA-based aptamer to impede protein aggregation properties of alpha-synuclein in a Parkinson's disease model

**Authors: *D. CHAN**;
Carleton Univ. Neurosci., Ottawa, ON, Canada

**Abstract:** Parkinson's disease (PD) is characterized by the accumulation of misfolded alpha-synuclein (aSyn) protein, which forms toxic aggregates leading to cellular death. Inhibition of aSyn aggregation represents a crucial therapeutic approach in PD. In this study, we aimed to characterize the in vitro properties of a DNA-based aptamer, asyn-2, that binds to aSyn monomers to prevent aggregation and reduce the spread of PD-associated pathology. Using an in vitro SH-SY5Y model system, we exposed the cells to aSyn preformed fibrils (PFFs) and examined the spatiotemporal pattern of aSyn aggregation. We then investigated the inhibitory effect of asyn-2 on aSyn aggregation in SH-SY5Y cells. Our results demonstrate that aSyn PFFs induced a dose- and time-dependent aggregation of aSyn in SH-SY5Y cells ($p < 0.001$). However, treatment with asyn-2 significantly reduced aSyn aggregation in SH-SY5Y cells, reaching a peak reduction of 46% ($p < 0.001$). These findings provide evidence for the potential of asyn-2 as a key therapeutic strategy for studying and halting PD pathology by targeting aSyn monomers to inhibit aSyn aggregation using exogenous aptamer treatments.

**Disclosures: D. Chan:** None.

**Poster**

**PSTR016. Alpha-Synuclein: Models**

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**Program #/Poster #:** PSTR016.13/J7

**Topic:** C.03. Parkinson's Disease

**Support:** Department of Veterans Affairs [Merit Review I01-BX003748 I01-BX005079

**Title:** Human Tissue-Engineered 3D Nigrostriatal Pathways: A Novel Approach to Understanding Synuclein Transport and Transmission in Parkinson's Disease

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**Abstract:** Parkinson's Disease (PD) is a progressive neurodegenerative disease characterized by degeneration of dopaminergic cells within the substantia nigra pars compacta (SNpc). As these cells degenerate, connectivity from the SNpc to the striatum through the nigrostriatal pathway becomes impaired, leading to a loss of dopamine in the striatum that causes the classic motor symptoms of PD. Accumulation of alpha-synuclein (α-syn) protein fibrils within axons and neuronal somata - leading to Lewy body formation - is the pathophysiological hallmark of PD. To better understand synucleinopathy, we have developed a three-dimensional anatomically-inspired *in vitro* model referred to as the tissue engineered nigrostriatal pathway (TE-NSP). The TE-NSP is biofabricated using human induced pluripotent stem cells (hiPSCs) differentiated into dopaminergic neurons and striatal neurons seeded at opposite ends of the lumen of a hydrogel micro-column generally spanning >1cm in length. Through a series of experimentation, we found that dopaminergic aggregates seeded at one end of the TE-NSP extended long bundled axonal tracts (>15 mm). When a population of medium spiny striatal neurons was added, we observed axonal-dendritic integration between the two discrete cell populations by 28 days *in vitro* (DIV). To explore the utility of the TE-NSP in probing mechanisms of synucleinopathy, we injected pre-formed α-syn fibrils (PFFs) and cultured TE-NSPs for 14 additional days. We found that at DIV 42, 50% of the dopaminergic neurons and 40 % striatal neurons within the treated TE-NSPs stained positive for α-syn- phosphorylated serine 129 (pS129) in comparison to only 1-5% of the respective neuronal populations in untreated controls. The presence of a pathological form of α-syn in the dopaminergic and the striatal neurons suggests intra-axonal α-syn transport and subsequent transmission to the striatal neurons. Co-staining of pS129 with tyrosine hydroxylase (TH) revealed significantly lower mean intensity of TH staining in the dopaminergic neurons of treated TE-NSPs in comparison to the untreated controls. Ongoing studies will further elucidate the mechanism of alpha-synuclein transmission between the two discrete neuronal populations. This novel approach of utilizing a tissue engineered brain pathway to mimic the fundamental aspects of PD using human neurons may be instrumental in understanding the key mechanisms of disease progression and neurodegeneration in PD patients.

**Disclosures: K.D. Browne:** None. **D. Chouhan:** None. **S. Karandikar:** None. **F. Laimo:** None. **R. Patel:** None. **D. Cullen:** Other; D.K. Cullen: D.K.C. is a scientific co-founder of Innervace Inc., a University of Pennsylvania spin-out company and is listed on U.S. Patent App. 15/032,677; U.S. Patent App. 16/093,036; 62/758,203. **J.E. Duda:** None.

**Poster**

**PSTR016. Alpha-Synuclein: Models**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR016.14/J8

**Topic:** C.03. Parkinson's Disease

**Support:** HBHL Grant 95014
HBHL Grant 95015
HBHL Grant 79082
CIHR
NSERC
FRQS

**Title:** Investigating the specificity of the prion-like spreading hypothesis of alpha-synuclein via a hippocampal disease epicenter in a longitudinal mouse model of synucleinopathy

**Authors: *J. PARK**[1,2], S. TULLO[1,2], D. R. GALLINO[2], E. DEL CID-PELLITERO[3], W. LUO[4], I. SHLAIFER[4], T. M. DURCAN[4], E. A. FON[3], M. CHAKRAVARTY[2,5,1,6];
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**Abstract:** Parkinson's Disease (PD) and other synucleinopathies are characterized by aggregation of toxic alpha-synuclein (αSyn) within Lewy bodies. Extensive research suggests a prion-like spreading of αSyn, but the mechanism for neurotoxicity mediated by this spreading is unclear yet crucial to developing therapeutics that halt disease progression. Recent work from our group demonstrated magnetic resonance imaging (MRI)-derived signatures of widespread brain atrophy upon striatal inoculation of pre-formed αSyn fibrils (PFF) in the M83 transgenic mouse model expressing the human αSyn A53T mutation (Tullo et al., 2022), suggesting a prion-like spread of pathology. Here, we test the specificity of this spread by inoculating another highly connected network hub; the hippocampus. Hemizygous (hemi) M83 mice were injected with 2.5 µL saline (PBS) or PFF into the right dorsal hippocampus (n=~5 group/sex/timepoint). Mice underwent in vivo MRI scanning (T1-weighted images; 100 µm³ isotropic voxels; 7T Bruker Biospec) at -7, 30, and 90 days post-injection. Neuroanatomical measures were obtained using deformation-based morphometry (DBM) with linear mixed effects model (LMER; fixed effects: treatment-by-days post-injection (dpi) interaction and sex; random effects: subject, scanner version, breeder supplier) analysis at the voxel level to assess whole-brain volumetric change longitudinally. Unlike our previous work demonstrating widespread atrophy after striatal injection, DBM results after FDR correction demonstrate significant focal volumetric reduction

of bilateral hippocampi in PFF-injected mice. Specifically, we observe significant reduction in the dentate gyrus, CA3 and CA1 (Fig.). Our results demonstrate a limited degree of prion-like spreading and atrophy after hippocampal PFF inoculation, possibly due to the choice of seed region (i.e.: the disease epicenter). These findings suggest that the whole-brain transmission of αSyn is particularly tuned to spreading through the motor network and may not be generalizable to disease epicenters in alternate network hubs.

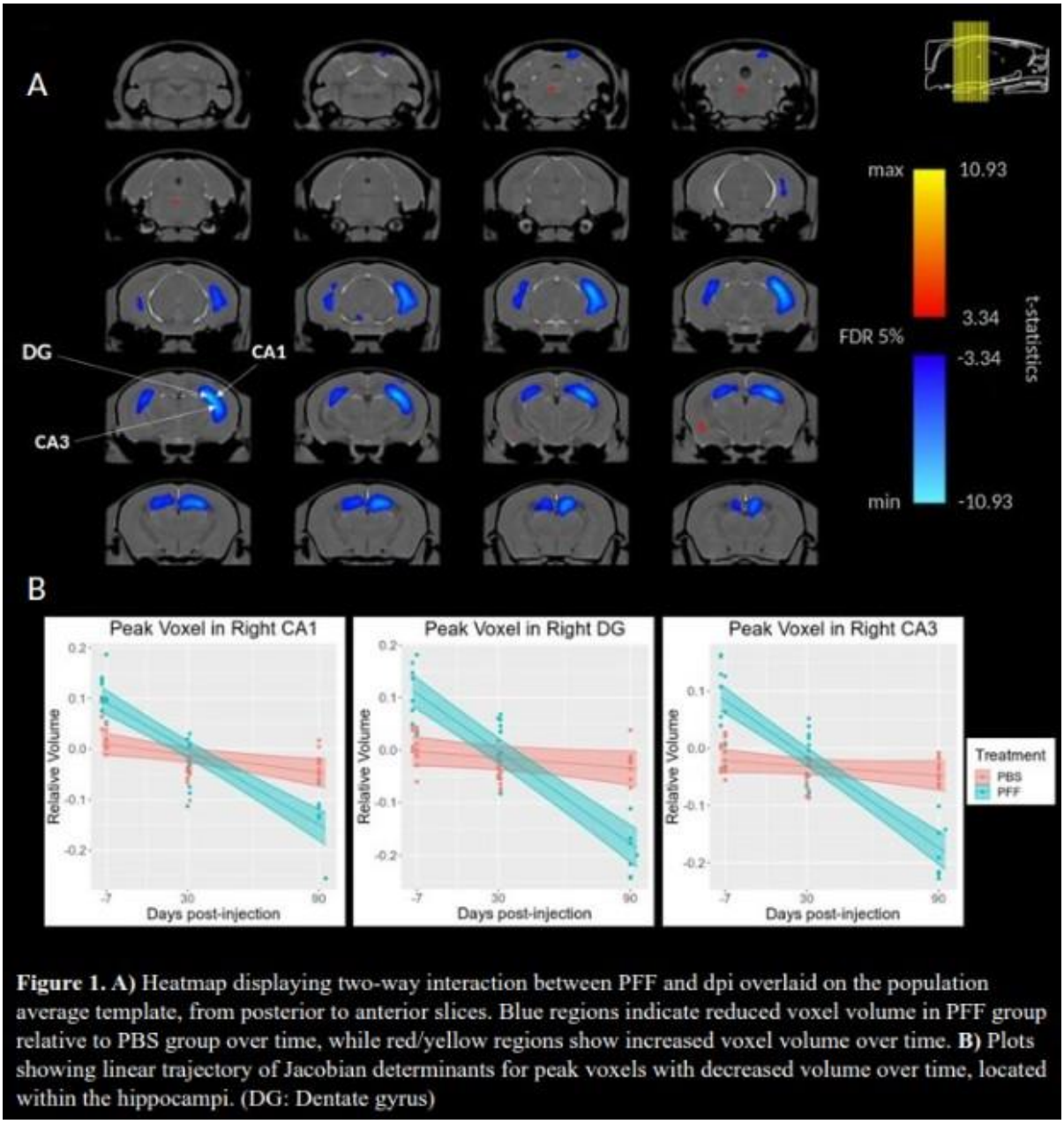


**Figure 1. A)** Heatmap displaying two-way interaction between PFF and dpi overlaid on the population average template, from posterior to anterior slices. Blue regions indicate reduced voxel volume in PFF group relative to PBS group over time, while red/yellow regions show increased voxel volume over time. **B)** Plots showing linear trajectory of Jacobian determinants for peak voxels with decreased volume over time, located within the hippocampi. (DG: Dentate gyrus)

**Disclosures: J. Park:** None. **S. Tullo:** None. **D.R. Gallino:** None. **E. del Cid-Pellitero:** None. **W. Luo:** None. **I. Shlaifer:** None. **T.M. Durcan:** None. **E.A. Fon:** None. **M. Chakravarty:** None.

**Poster**

**PSTR016. Alpha-Synuclein: Models**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR016.15/J9

**Topic:** C.03. Parkinson's Disease

**Support:** Doctoral School of Health, University of Helsinki
Finnish Parkinson Foundation
Orion Research Foundation
Doctoral Programme in Drug Research, University of Helsinki

**Title:** Gdnf reduces alpha-synuclein accumulation after delivery of lactacystin and pre-formed fibrils, in vitro and in mice

**Authors: *S. ER**[1], I. PARKKINEN[1], A. SEELBACH[2], S. PASCULLI[2], F. DE LORENZO[1], K. C. LUK[4], P. CHMIELARZ[5], A. DOMANSKYI[3], M. AIRAVAARA[1];
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**Abstract:** Dysfunctions in protein degradation pathways are listed among the underlying causes of many neurodegenerative conditions, like Parkinson's disease. A hallmark autopsy finding in the brain of Parkinson's disease patients is neuronal Lewy pathology. Lewy bodies are insoluble inclusions containing modified alpha-synuclein protein. GDNF, a growth factor, can eliminate the formation of pre-formed fibril (PFF)-seeded Lewy body-like inclusions in dopamine neurons. We examined GDNF's effects, *in vitro* and *in vivo*, with models combining proteasome inhibition by lactacystin and PFF-induced alpha-synuclein aggregation in the midbrain neurons. PFF-seeded midbrain cultures were incubated with lactacystin for 1 or 2 days. At both time points and with varying concentrations, the drug was highly detrimental to dopamine neurons. Lactacystin did not cause the formation of Lewy body-like inclusions in dopamine neurons in the absence of PFFs. However, in the presence of PFFs, lactacystin treated cultures had less of these inclusions. While GDNF was not protective against lactacystin-induced neurodegeneration, it continued to attenuate the formation of alpha-synuclein aggregation in the surviving neurons. *In vivo,* control or AAV-GDNF vectors were infused into the region above the substantia nigra of mice (N=80). A week later, the mice were unilaterally injected with PFFs to the striatum and lactacystin to the midbrain. Animals were sacrificed 2 weeks after the PFF/lactacystin injections. Behavioral tests performed after the treatments showed significant motor asymmetry for most of the mice. Spontaneous activity of mice that received both lactacystin and PFFs, but not AAV-GDNF, was significantly reduced. Similar to our *in vitro* findings, lactacystin did not cause Lewy-like pathology *in vivo* in the absence of PFFs, at least at the tested time point, whereas GDNF attenuated PFF-induced alpha-synuclein pathology in the midbrain, even in the presence of lactacystin. Immunohistochemical staining could only partly explain the behavioral results. Infusion of AAV-GDNF above the substantia nigra resulted in DAT and TH downregulation in the brain dopaminergic system. These findings show that GDNF can eliminate Lewy body-like pathology even in the presence of proteasomal inhibitor and that GDNF effects is at least partly

independent of proteosome activity. Hence, activation of GDNF signaling pathways can be protective against the formation of Lewy bodies in Parkinson's disease brain. Novel therapies targeting protein aggregation in the disease should consider the interplay with the modulation of protein homeostasis.

**Disclosures: S. Er:** None. **I. Parkkinen:** None. **A. Seelbach:** None. **S. Pasculli:** None. **F. De Lorenzo:** None. **K.C. Luk:** None. **P. Chmielarz:** None. **A. Domanskyi:** None. **M. Airavaara:** None.

**Poster**

**PSTR016. Alpha-Synuclein: Models**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR016.16/J10

**Topic:** C.03. Parkinson's Disease

**Support:** European Research Council Starting Grant 805426
Academy of Finland Grant
Sigrid Jusélius Foundation
Finnish Parkinson Foundation
University of Helsinki Doctoral School Grant

**Title:** The combination of alpha-synuclein pre-formed fibrils and a mitochondrial toxin to model Parkinson's disease in mice and the effect of CDNF in it

**Authors: *A. SINGH**[1], A. PANHELAINEN[1], S. REUNANEN[1], K. C. LUK[2], M. H. VOUTILAINEN[1];
[1]Fac. of Pharm., Univ. of Helsinki, Helsinki, Finland; [2]Dept. of Pathology and Lab. Med., Univ. of Pennsylvania, Philadelphia, PA

**Abstract:** Parkinson's disease (PD) is characterized by loss of dopamine (DA) neurons in the nigrostriatal tract and manifests as motor deficits in patients. The histological hallmark of the disease is the presence of intraneuronal inclusions called Lewy bodies, which are primarily composed of alpha-synuclein (aSyn) protein. Irrespective of the complexity of PD, the available pre-clinical models of the disease recapitulate only limited disease characteristics. The development of more holistic models could improve testing of candidate drugs and their interaction with different pathological features of the disease.
In our study, we tested a combination of aSyn pre-formed fibrils (PFFs) and a mitochondrial toxin to develop a mouse model of PD exhibiting both Lewy body-like aSyn aggregation and DA neuron loss in a feasible timeframe. 7-9 weeks old C57BL/6J mice received unilateral, intrastriatal injections of PFF and the toxin at an interval of 2 weeks and were sacrificed after 14 weeks. Furthermore, we studied the possible neurorestorative effects of cerebral dopamine neurotrophic factor (CDNF) in this model. It has been reported to provide neurorestoration in toxin rodent models of PD and to interact with aSyn both in vivo and in vitro. In our study,

CDNF was injected intrastriatally 2 weeks after toxin injection. The pathology was assessed by quantifying the DA neurons and phosphorylated aSyn (paSyn)-positive inclusions. Behavioural tests were conducted at regular intervals to assess the motor function of these mice.
We found that at 14 weeks timepoint, the PFF + toxin-injected mice had significant loss of DA neurons in the substantia nigra and their fibers in the striatum. This was observable in the amphetamine-induced rotation test where these combination-injected mice rotated significantly more than the control group. There was also the presence of paSyn aggregates in these animals. The single intrastriatal injection of CDNF was neither able to restore the nigrostriatal system nor affect the aSyn pathology in this robust PD model. However, at behavioral level, in cylinder test, the paw-usage bias was alleviated in CDNF-treated mice compared to the combination-injected mice.
We conclude that the combination model of PFF + toxin is a viable option to mirror the PD pathology in mice. Additionally, we speculate that the dosing of CDNF was not sufficient and that multiple dosing or chronic infusions of the protein could lead to better neurorestorative effects. With this study, we shed light on the complexity of experimental disease modeling for multifactorial diseases such as PD and assert the need for multi-stressor models recapitulating more than one feature of the disease.

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**Poster**

**PSTR016. Alpha-Synuclein: Models**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR016.17/K1

**Topic:** C.03. Parkinson’s Disease

**Support:** Huffington Foundation

**Title:** Alpha synuclein G51D knock-in mice display olfactory deficit, gastrointestinal dysfunction, and motor dysfunction

**Authors: *Y. KIM**[1,4], J. MCINNES[1,4], J. KIM[1,4], Y. W. LIANG[1,4], S. VEERARAGAVAN[1,4], B. BELFORT[1,4], A. GARZA[1,4], B. ARENKIEL[1,4], R. SAMACO[1,4], H. Y. ZOGHBI[1,4,2,3,5];
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**Abstract:** Parkinson’s disease (PD) is characterized by motor and non-motor function deficit with neuropathological characterization of Lewy body in the brain, which is composed of phosphorylated, insoluble alpha synuclein (SNCA). Single amino acid changes in the alpha synuclein gene can cause familiar early onset PD. To date, most synucleinopathy mouse models

involve overexpression of α-synuclein-encoding cDNA driven by a heterologous promoter. To understand the pathogenesis of α-synuclein driven PD, we hypothesized that a knock-in (KI) of a disease-causing mutation into the Scna locus in mice will permit better assessment of regional vulnerability and phenotypic progression. To this end, we generated three different *Scna* point mutation KI mouse models (*Snca*$^{A30P}$, *Snca*$^{E46K}$, and *Snca*$^{G51D}$). The *Snca*$^{G51D}$ KI mice, out of the three different KI models, shows the most noticeable difference in the motor behavior test from 9 months of age. Before the age of behavioral deficits appeared, homozygous *Snca*$^{G51D}$ animals display abnormalities in olfactory function and slower gut transit time from 6 months, showing early non-motor symptoms of PD. They also exhibit phospho-S129 α-syn positive staining in olfactory tissue, cerebral cortex, entorhinal cortex, enteric nerve in the colon and dorsal motor neuron of vagus nerve from 3 months of age, where early alpha synuclein pathology found in PD. These findings suggest that the *Snca*$^{G51D}$ KI mouse model is a useful tool for studying biology of α-syn related diseases in mice.

**Disclosures: Y. Kim:** None. **J. McInnes:** None. **J. Kim:** None. **Y.W. Liang:** None. **S. Veeraragavan:** None. **B. Belfort:** None. **A. Garza:** None. **B. Arenkiel:** None. **R. Samaco:** None. **H.Y. Zoghbi:** None.

**Poster**

**PSTR016. Alpha-Synuclein: Models**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR016.18/K2

**Topic:** C.03. Parkinson's Disease

**Support:** Natural Science foundation of Jiangsu Province (BK20221155)

**Title:** The role of different SNCA mutation in Parkinson's disease as revealed by comparing 2 mice models

**Authors:** H. QI[1], F. LIU[1], Z. LI[2], Z. LAI[1], X. HU[1], ***S. BHAVE**[2], C. JU[1], J. ZHAO[1], X. GAO[1]; [1]GemPharmatech CO., Ltd., Nanjing, China; [2]GemPharmatech LLC, La Jolla, CA

**Abstract:** Parkinson's disease (PD) is a prevalent neurodegenerative disorder that affects millions of people. SNCA encodes alpha-synuclein, and is frequently mutated in familial PD patients. Studies have shown that distinct SNCA mutations influence alpha-synuclein aggregation and PD pathology by altering the fibril structure. In order to investigate how SNCA mutations affect PD pathology in vivo, we generated transgenic mouse models for SNCA E46KA53T (B6-hSNCAM2) and SNCA A53T (B6-hSNCAM1) based on C57BL/6 mice. We systematically evaluated the characteristics of B6-hSNCAM2 and B6-hSNCAM1 mice and observed that both models exhibited PD-like phenotypes. Pathological examinations revealed that B6-hSNCAM2 exhibited more severe loss of TH+ neurons and accumulation of alpha-synuclein compared to B6-hSNCAM1, as indicated by immunohistochemical analysis. Moreover, B6-hSNCAM2 presented with motor deficits that were significant before 3 months of

age, whereas B6-hSNCAM1 exhibited comparable symptoms at 4 months of age. Interestingly, in contrast to B6-hSNCAM1 mice, B6-hSNCAM2 mice displayed an early onset of motor deficits but had a slower disease course and survival endpoint. In conclusion, the results suggest that various SNCA mutations may have an impact on the pathological and behavioral progression of PD in vivo, leading to distinct features of disease progression.

**Disclosures:** **H. Qi:** None. **F. Liu:** None. **Z. Li:** None. **Z. Lai:** None. **X. Hu:** None. **S. Bhave:** None. **C. Ju:** None. **J. Zhao:** None. **X. Gao:** None.

**Poster**

**PSTR016. Alpha-Synuclein: Models**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR016.19/K3

**Topic:** C.03. Parkinson's Disease

**Support:** VLAIO Grant HBC.2020.2901

**Title:** Pff and/or viral vector based models for preclinical proof of concept studies targeting alpha-synuclein pathology

**Authors:** S. CARMANS[1], E. VONCK[2], ***W. DEJONCKHEERE**[3], V. BAEKELANDT[2], T. CORNELISSEN[1];
[1]reMYND, Leuven, Belgium; [2]KU Leuven, Lab. for Neurobio. and Gene Therapy, Leuven, Belgium; [3]reMYND nv, Leuven, Belgium

**Abstract:** Parkinson's disease (PD) is the most common neurodegenerative movement disorder and is characterized by the accumulation of alpha-synuclein protein aggregates in the PD brain. These inclusions, accompanied with the degeneration of dopaminergic neurons are the neuropathological hallmarks of this incurable disease. Currently a lot of effort is put into studying the involvement of different forms of alpha-synuclein, i.e. monomeric, oligomeric, fibrillar and aggregated forms or different post translational modifications of the protein, and their contribution to disease progression. Targeting alpha-synuclein thus has an important therapeutic value. Since the research field lacks good and consistent animal models for preclinical research, we are developing mouse models based on the administration of sonicated preformed fibrils (PFF), either alone or in combination with viral vectors. Unilateral and bilateral stereotactical injections in the dorsal striatum of young wild type mice with sonicated mouse PFF's showed clear pathology and robust neurodegeneration at varying time points (4-13 weeks) after PFF administration. Since an increasing interest in more translational models is observed, and treatments are targeting human alpha-synuclein specifically, the development of models combining human PFF's and expression of human alpha synuclein via viral vectors is initiated. Different administration routes (including intrathecal, intravenous and stereotactical injections) using different AAV vectors were explored. Since combined administration of hPFF and AAV2/7-human-aSyn did not worsen the previously described phenotype observed by Oliveras-

Salvá et al; 2013, newly developed AAV vectors expressing GFP were injected either intrathecal or intravenous and the GFP expression levels were assessed to define the region and level of protein expression. Depending on the outcome we will combine the most efficient viral vector with administration of human PFF's to induce seed and spread pathology of human alpha-synuclein. These alpha-synuclein based models can be of great importance to the research field to assess in vivo therapeutic interventions based on targeting human alpha-synuclein pathology and more specifically the spreading of human alpha-synuclein.

**Disclosures:** **S. Carmans:** A. Employment/Salary (full or part-time); reMYND. **E. Vonck:** None. **W. Dejonckheere:** A. Employment/Salary (full or part-time); reMYND. **V. Baekelandt:** A. Employment/Salary (full or part-time); KU Leuven. **T. Cornelissen:** A. Employment/Salary (full or part-time); reMYND.

**Poster**

**PSTR016. Alpha-Synuclein: Models**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR016.20/K4

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

**Support:** Mayo Alzheimer's Disease Research Center Developmental Grant (to N.Z.)
Lewy Body Dementia Center Without Walls U54NS110435 (to D.W.D., P.J.M., O.A.R., G.B., and N.Z.)
The Ed and Ethel Moore Alzheimer's Disease Research Program Fellowship (to Y.J.)

**Title:** Modeling Synucleinopathies with SNCA Triplication iPSC-Derived Cortical Organoids and Identifying Therapeutic Drugs

**Authors:** ***Y. JIN**, F. LI, Z. LI, T. C. IKEZU, J. O'LEARY, Y. ZHU, Y. A. MARTENS, S. KOGA, Y. LI, W. LU, Y. YOU, K. LOLO, M. DETURE, M. DAVIS, P. J. MCLEAN, O. ROSS, T. KANEKIYO, T. IKEZU, Z. WSZOLEK, G. BU, D. W. DICKSON, N. ZHAO; Mayo Clin., Jacksonville, FL

**Abstract:** The aggregation of α-synuclein (α-SYN), which is encoded by the *SNCA* gene, is the pathological hallmark of synucleinopathy, including Lewy body disease (LBD). LBD affects various neuronal subtypes in distinct brain regions, such as dopaminergic neurons in the midbrain associated with Parkinson's disease (PD), as well as excitatory neurons in the cortical regions linked to dementia with Lewy bodies (DLB). However, our understanding of the pathophysiology of α-SYN in LBD, particularly in excitatory neurons, remains limited. In this study, we generated human cortical synucleinopathy models by differentiating induced pluripotent stem cells (iPSCs) derived from LBD patients with *SNCA* gene triplication into cerebral organoids. After two-month culture period, we observed significantly elevated levels of

total α-SYN, phosphorylated α-SYN, and aggregated α-SYN in the *SNCA* triplication organoids compared to control organoids. Notably, single-cell RNA sequencing (scRNA-seq) analysis revealed that the *SNCA* gene was predominantly expressed in excitatory neurons. Pathway analysis of scRNA-seq data indicated synaptic and mitochondrial dysfunction as the top pathways associated with *SNCA* triplication, which we further validated through measurements of neuronal activity using multi-electrode array (MEA) and mitochondrial respiration using Seahorse analysis. To strengthen the relevance of our organoid model for studying α-SYN pathogenesis, we performed single-nucleus RNA sequencing analysis on the superior temporal cortex of human LBD brains, including carriers with *SNCA* duplication and triplication. Our findings from human LBD brains corroborated the observations from the organoid model, further supporting the utility of our approach. To address α-SYN aggregation, we screened FDA-approved drugs and identified potential inhibitors of α-SYN seeding using the Real-Time Quaking-Induced Conversion (RT-QuIC) assay. Four drugs significantly reduced α-SYN aggregates and alleviated mitochondrial dysfunction in *SNCA* triplication organoids. Altogether, our study provides insight into cortical synucleinopathy models and the discovery of drugs targeting α-SYN aggregation in LBD.

**Disclosures:** **Y. Jin:** None. **F. Li:** None. **Z. Li:** None. **T.C. Ikezu:** None. **J. O'Leary:** None. **Y. Zhu:** None. **Y.A. Martens:** None. **S. Koga:** None. **Y. Li:** None. **W. Lu:** None. **Y. You:** None. **K. Lolo:** None. **M. DeTure:** None. **M. Davis:** None. **P.J. McLean:** None. **O. Ross:** None. **T. Kanekiyo:** None. **T. Ikezu:** None. **Z. Wszolek:** None. **G. Bu:** None. **D.W. Dickson:** None. **N. Zhao:** None.

**Poster**

**PSTR017. Other Motor Neuron Diseases: SMA, SBMA, and Childhood ALS**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR017.01/K5

**Topic:** C.06. Neuromuscular Diseases

**Support:** NIH RO1 NS078375-06 (G.Z.M.)
AFM Téléthon #19655

**Title:** Serotonergic dysfunction impairs locomotor coordination in spinal muscular atrophy

**Authors: *N. DELESTRÉE**, E. SEMIZOGLOU, J. G. PAGIAZITIS, A. VUKOJICIC, E. DROBAC, V. PAUSHKIN, G. Z. MENTIS;
Columbia Univ., New York, NY

**Abstract:** Neuromodulation by serotonin (5-HT) regulates the activity of neuronal networks responsible for a variety of essential behaviors. 5-HT is intricately involved in the production of locomotor activity and gait control. Although dysfunction of serotonergic neurotransmission has been associated with mood disorders and spasticity after spinal cord injury, whether and to what extent such dysregulation is implicated in diseases affecting motor control has not been firmly

established.Here, we investigated whether 5-HT neuromodulation is affected in spinal muscular atrophy (SMA), a neurodegenerative disease caused by ubiquitous deficiency of the SMN protein. The hallmarks of SMA are death of motor neurons, muscle atrophy, and impaired motor control, both in humans and mouse models of disease. We utilized the SMNΔ7, a severe SMA mouse model, that recapitulates the symptoms of Type I SMA patients, the most common form of the disease.Utilizing mouse genetics, optogenetics, physiology, morphology, and behavioral analysis, we report a severe dysfunction of 5-HT neurotransmission in the spinal cord of SMA mice, both at early and late stages of disease. We found that the modulatory effect of serotonin on the monosynaptic spinal reflex is reduced by up to 80% in SMA. This dysfunction is followed by reduction of 5-HT synapses on both somatic and dendritic compartments of vulnerable motor neurons. We demonstrate that motor neurons innervating axial and trunk musculature are preferentially affected compared to the those innervating distal muscles, suggesting a possible cause for the proximo-distal progression of disease. We also demonstrate that the 5-HT dysfunction is caused by SMN deficiency in serotonergic neurons themselves in the raphe nuclei. The behavioral significance of the dysfunction in serotonergic neuromodulation is underlined by inter-limb discoordination in SMA mice, suggesting dysregulation of the neuromodulation at the motor circuit level. The locomotor discoordination is greatly ameliorated following selective genetic restoration of SMN in 5-HT neurons.Our study uncovers an unexpected dysfunction of serotonergic neuromodulation in SMA and indicates that, if normal function is to be restored under disease conditions, 5-HT neuromodulation should be a key target for therapeutic approaches.

**Disclosures:** **N. Delestrée:** None. **E. Semizoglou:** None. **J.G. Pagiazitis:** None. **A. Vukojicic:** None. **E. Drobac:** None. **V. Paushkin:** None. **G.Z. Mentis:** None.

**Poster**

**PSTR017. Other Motor Neuron Diseases: SMA, SBMA, and Childhood ALS**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR017.02/K6

**Topic:** C.06. Neuromuscular Diseases

**Support:** JSPS Grant 21K11188

**Title:** Characterization of the trigeminal ganglion in mouse models of spinal muscular atrophy ($Smn^{2B/-}$ and $Smn^{-/-}$;SMN2)

**Authors:** ***T. SATO**[1], K. SHIMAZAKI[1], T. YAJIMA[1], D. TACHIYA[1], Y. DE REPENTIGNY[2], R. KOTHARY[2], H. ICHIKAWA[1];
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**Abstract:** Spinal muscular atrophy (SMA) is a neuromuscular disease of young children that leads to motor neuron death in the spinal cord and atrophy of their innervating muscles. SMA is

caused by mutations of deletions of the survival motor neuron 1 (*SMN1*) gene. Interestingly, SMN deficiency has little or no effect on sensory neurons. The number of sensory neurons is similar in the dorsal root ganglia of wildtype and *Smn*$^{-/-}$*;SMN2* mice. However, little is known about the effect of SMN deficiency on sensory neurons in the trigeminal nervous system. In this study, we investigated the number and cell size of sensory neurons in the trigeminal ganglion (TG) of two different mouse models of SMA, namely *Smn*$^{2B/-}$ and *Smn*$^{-/-}$*;SMN2* mice. Three wildtype and 3 *Smn*$^{2B/-}$ mice at postnatal day 21 were used in this study. Five C57BL/6 wildtype and 5 *Smn*$^{-/-}$*;SMN2* mice at postnatal day 5 were also investigated. These animals were deeply anesthetized with tribromoethanol (Avertin) and transcardially perfused with 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4). The TG was dissected, frozen-sectioned at 8 μm thickness and processed for Nissl stain. By a macroscopic analysis, the TGs in wildtype mice were large and had 2 thick nerves, the opthalmo-maxillary and mandibular nerves. The TG in *Smn*$^{2B/-}$ mice also had a large ganglionic body, and thick opthalmo-maxillary and mandibular nerves. In *Smn*$^{-/-}$*;SMN2* mice, however, the length, width and thickness of the TG was severely decreased and the two nerves were small. At the microscopic level, numerous sensory neurons were detected in the TG of wildtype mice. These neurons mainly had small and medium-sized cell bodies. *Smn*$^{2B/-}$ mice showed no remarkable change in the number and cell size of TG neurons. In *Smn*$^{-/-}$*;SMN2* mice, however, the number of sensory neurons dramatically decreased in the TG. Many TG neurons with medium-sized to large cell bodies disappeared in *Smn*$^{-/-}$*;SMN2* mice. These findings suggest that the different severity of disease in the two mouse models have different effects on the TG during developmental stages.

**Disclosures:** **T. Sato:** None. **K. Shimazaki:** None. **T. Yajima:** None. **D. Tachiya:** None. **Y. De Repentigny:** None. **R. Kothary:** None. **H. Ichikawa:** None.

**Poster**

**PSTR017. Other Motor Neuron Diseases: SMA, SBMA, and Childhood ALS**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR017.03/Web Only

**Topic:** C.06. Neuromuscular Diseases

**Support:** KAKENHI JP 19K07970

**Title:** Kaempferol promotes the degradation of mutant proteins via a novel mTOR-dependent autophagic pathway

**Authors: *H. ADACHI**[1], Z. HUANG[1], T. TOYOTA[1], Q. QIANG[2], M. KATSUNO[3], G. SOBUE[4];
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**Abstract:** In chronic neurodegenerative diseases, such as spinal and bulbar muscular atrophy (SBMA) commonly observed phenotypes include the abnormal accumulation of disease-causing proteins and the formation of nuclear and cytoplasmic inclusions. We examined the effects of the natural flavonoid kaempferol in cultured cell models of neurodegenerative diseases expressing mutant androgen receptor (AR), huntingtin, atrophin-1 and ataxin-1. We administrated kaempferol to AR-24Q and AR-97Q SBMA transgenic mice at doses of 0 mg/kg or 30mg/kg respectively everyday via oral gavage from age 6 to 30 weeks and examined various neurological and behavioral parameters.Kaempferol preferentially decreased the expression of those causative proteins in the neuronal cell models. The expression levels of the autophagic marker LC-3 II and phospho-beclin-1 were significantly elevated in the cells after treatment with kaempferol. Kaempferol also decreased the expression of p62. Kaempferol treatment showed improvement of motor dysfunction, alleviated body weight loss and enhanced survival rate in comparison with vehicle treated SBMA transgenic mice.These findings demonstrated that kaempferol induced autophagosome formation and enhanced the preferential degradation of the disease-causative proteins, and is a potential therapeutic reagent for the prevention of neurodegenerative diseases associated with the accumulation of polyQ-expanded proteins.

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**Poster**

**PSTR017. Other Motor Neuron Diseases: SMA, SBMA, and Childhood ALS**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR017.04/K7

**Topic:** C.06. Neuromuscular Diseases

**Support:** NIH Grant R15NS120154
G-RISE T32GM144895
COBRE 5P20GM103653
RISE R25GM122722

**Title:** The SMNΔ7 mouse model for spinal muscular atrophy exhibits no significant sex-specific phenotypic differences

**Authors: *N. COTTAM**, M. HARRINGTON, P. SCHORK, J. SUN;
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**Abstract:** Spinal muscular atrophy (SMA) is an autosomal recessive disease that affects 1 out of every 6,000-10,000 individuals at birth, making it the leading genetic cause of infant mortality. A deletion or mutation in survival motor neuron 1 (SMN1) gene, the disease-determining gene for SMA, results in lower motor neuron dysfunction and degeneration, leading to progressive muscle atrophy, weakness, and paralysis. There are 5 subtypes of SMA, type 0 to 4, which differ by SMN2 copy number of SMN2 and age of onset. However, there is substantial genetic

heterogeneity across these subtypes, which can be explained, at least in part, by a number of disease-modifying genes that are both SMN-dependent and -independent. Among these are several genes encoded exclusively on the X chromosome, such as plastin 3, Ubiquitin Specific Peptidase 9 X-Linked, and Ubiquitin Like Modifier Activating Enzyme. In many other neurodegenerative disorders, sex is a significant risk factor. Reports of sex differences in SMA patients are largely inconsistent or incomplete, with some studies pointing to a higher severity and occurrence rate for males, and some reporting no sex differences altogether. To date, when employing animal models to study SMA such as the SMNΔ7 mouse model, sex as a contributing biological variable has been largely overlooked. The popular SMNΔ7 mouse model of severe SMA is regularly employed to investigate pathologies and test therapeutic effectiveness. However few studies have compared sex differences, and they do not point conclusively to one answer.
In this study, we investigated differences in SMA occurrence, lifespan, and phenotype between male and female mice of the SMNΔ7 strain. To do this, 23 mouse litters were tracked and common phenotypic assessments, including body and brain weights, righting reflex, and negative geotaxis task were performed. We found that the likelihood of a male or female pup being SMA-affected does not differ significantly, survival periods are the same across sexes, and that sex is not a significant source of phenotypic variation in mice. Overall, this study affirms that sex is not a biological variable that contributes to differences in disease severity in the SMNΔ7 mouse model, and thus does not have to be controlled when planning experiments with this model.

**Disclosures:** **N. Cottam:** None. **M. Harrington:** None. **P. Schork:** None. **J. Sun:** None.

**Poster**

**PSTR017. Other Motor Neuron Diseases: SMA, SBMA, and Childhood ALS**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR017.05/Web Only

**Topic:** C.06. Neuromuscular Diseases

**Support:** BIOGEN project TW-SPN-11591

**Title:** Effects and mechanisms of nusinersen treatment in a mouse model of adult spinal muscular atrophy at the late stage

**Authors: *L.-K. TSAI**[1,3], H.-J. LAI[1], C.-H. KAO[1], Y.-C. TSAI[1], S.-T. TAI[1], W.-C. WENG[2]; [1]Dept. of Neurol., [2]Dept. of Pediatrics, Natl. Taiwan Univ. Hosp., Taipei City, Taiwan; [3]Dept. of Neurol., Natl. Taiwan Univ. Hosp. Hsinchu branch, Hsinchu City, Taiwan

**Abstract: Background:** Spinal muscular atrophy (SMA) is a hereditary progressive motor neuron disease. Nusinersen, an antisense oligonucleotide, targeting *SMN2* gene is effective in both children and adults with SMA. It is surprising that about two fifth of adult SMA patients not only showed stabilization of disease but demonstrated meaningful motor functional improvement after nusinersen treatment. However, the mechanisms behind such a benefit are still unclear.

**Rationale:** We used a mouse model of adult SMA at the late stage to fully represent adult SMA patients and avoid influence by neuromuscular development and plasticity at young age. This study is aimed to investigate the effects and mechanisms of nusinersen treatment in adult SMA mice at the late stage with emphasis on status of spinal motor neuron and neuromuscular junction (NMJ). **Methods:** Adult SMA mice (*Smn-/-SMN2+/+*) were treated with two shoots of nusinersen (each 2 μg/g) or normal saline (control) via stereotaxic injection into cerebroventricle at the age of 12 and 13 months and were sacrificed at 14 months. Each mouse received monthly motor function assessment using rotarod maintenance test from the age of 11 to 14 months. Nerve conduction study was conducted on sciatic nerves to analyze motor unit number estimation (MUNE) before and after treatment. The pathology of lumbar spinal cord and hamstrings muscle were investigated using immunohistochemistry for motor neuron density and architecture of neuromuscular junctions (NMJs). The pathology of adult SMA mice at 12 months of the age was used to represent pre-treatment conditions. **Results:** Nusinersen treatment led to dose dependent increase of SMN protein and transcripts in brain and spinal cord. SMA mice that received nusinersen treatment showed significant improvement in motor functions using rotarod maintenance test at both accelerated and fixed modes. Nusinersen treatment increased MUNE in adult SMA mice while untreated SMA mice revealed a trend toward reduction of MUNE. At 14-month-old, nusinersen-treated SMA mice showed similar spinal motor neuron density as compared to untreated SMA mice; however, nusinersen treatment prevented reduction of density of spinal motor neurons having axons innervating muscles. In addition, nusinersen treatment not only prevented NMJ denervation, but promoted NMJ innervation in late-stage adult SMA mice. **Conclusion:** Nusinersen treatment can improve motor function in late-stage adult SMA mice, via mechanisms of enhancement in NMJ innervation and increase of functional motor neuron number, namely activation of functionless but still alive motor neurons to functional motor neurons.

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**Poster**

**PSTR017. Other Motor Neuron Diseases: SMA, SBMA, and Childhood ALS**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR017.06/K8

**Topic:** C.06. Neuromuscular Diseases

**Support:** Roche support

**Title:** Three dimension stem cell spinal cord model to study the therapeutic mechanisms of risdiplam-like compound for spinal muscular atrophy.

**Authors:** A. D'ANGELO[1], F. BEATRICE[1], J. ONGARO[2], P. RINCHETTI[1], I. FARAVELLI[1], M. MIOTTO[3], S. LODATO[3], M. NIZZARDO[2], G. P. COMI[1,2], L. OTTOBONI[1], ***S. CORTI**[1,2]; [1]Univ. of Milan, Milan, Italy; [2]Fndn. IRCCS Ca' Granda Maggiore Policlinico Hosp., Milan, Italy; [3]Humanitas Clin. and Res. Ctr., Milan, Italy

**Abstract:** Spinal Muscular Atrophy (SMA) is a severe neurological disorder characterized by early onset and degeneration of lower motor neurons due to mutations in the *SMN1* gene. To reproduce reliable human models, we generated and phenotypically characterized human spinal cord organoids from induced pluripotent stem cells (iPSCs) of SMA type 1 subjects (n=3) and healthy controls (n=2). Our study aimed at improving the treatment of SMA by investigating the efficacy of a Risdiplam-like compound on 3-dimensional (3D) spinal cord model. Treatment, whose main action is restoring SMN protein level, was started at different time points during the first 80 days of organoid development which parallels the first trimester post conception and was provided as daily therapy every two days. We observed that SMA samples present a pervasive cellular and molecular developmental alteration in multiple cell populations, including neural progenitors, beyond motor neurons. This was ascertained using bulk transcriptomics, single cells RNAseq, and multi-electrodes array analysis, along with immunophenotypic characterization. Our preliminary results on treatment demonstrated that 1) Risdiplam-like compound modulates at least 15% of disease affected genes; 2) long-term *in vitro* treatment is well-tolerated; 3) ratio between full length *SMN2* and *Δ7* is robustly restored; 4) pathological hallmarks are reverted, all in all supporting the idea that SMA organoids represent a reliable model to explore drug kinetics and therapeutic consequences. Moreover, our study highlights the early-onset and pervasive developmental nature of SMA pathogenesis, which can be further disentangled exploiting organoids. Optimizing Risdiplam-like therapy for all SMA patients and developing combined therapeutic approaches is a key aspect in clinical perspective and can be achieved by understanding the whole drug mechanisms of action. Our study precisely contributes to the optimization of Risdiplam therapy and to the identification of targets for complementary treatment intervention in SMA patients.

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**Poster**

**PSTR017. Other Motor Neuron Diseases: SMA, SBMA, and Childhood ALS**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR017.07/K9

**Topic:** C.06. Neuromuscular Diseases

**Support:** Italian Ministery of Health Grant

**Title:** Targeted antisense oligonucleotide treatment rescues developmental alteration in spinal muscular atrophy organoids

**Authors: *P. RINCHETTI**[1], I. FARAVELLI[3], M. TAMBALO[4], I. SIMUTIN[4], S. MANCINELLI[4], L. MAPELLI[5], M. MIOTTO[4], A. D'ANGELO[6], M. RIZZUTI[9], E. D'ANGELO[5], G. P. COMI[7], S. PRZEDBORSKY[2], S. LODATO[4], M. NIZZARDO[6], S. CORTI[8]; [1]Syst. Biol., Columbia Univ., NEW YORK, NY; [2]Columbia Univ., New York, NY; [3]Harvard Univ., Cambridge, MA; [4]Humanitas Res. Hosp., Milan, Italy; [5]Univ. of Pavia, Pavia, Italy; [6]Univ. of Milan, Milan, Italy; [7]Univ. of Milan, Fondazione IRCCS Ca' Granda O, Univ. of Milan, Milano, Italy; [8]Univ. of Milan, Univ. of Milan, Milan, Italy; [9]IRCCS Policlinico, IRCCS Policlinico Hosp., Milan, Italy

**Abstract:** Spinal Muscular Atrophy (SMA) is an autosomal-recessive disorder caused by mutations in the *SMN1* gene, leading to an early onset and degeneration of cells in the ventral horn of the spinal cord. Although ubiquitous expression of SMN, lower motor neurons are the most vulnerable neuronal type to protein decreasing, with a resulting clinical phenotype of progressive muscular atrophy. Recently, breakthrough therapeutic strategies developed to restore the levels of SMN have received FDA/EMA approval and are currently in clinical use; altogether have dramatically changed the clinical prognosis of SMA. Although growing clinical data show that approved treatments also provide benefits in the chronic phase, an unmet therapeutic need remains for patients treated after symptom onset, and it is not yet clear which are the interfering factors with the efficacy of the treatment. In addition, explanations for the observed variability in treatment response along with the impact on tissues other than the spinal cord still need to be addressed. Therefore, a better understanding of SMA mechanisms in the early disease stages, even prenatally, is pivotal to optimizing current therapeutic approaches by increasing efficiency, targeting/biodistribution, and developing new clinical strategies.Moreover, it is necessary to understand SMN's role in reliable biological models to optimize the available treatments and facilitate the development of novel compounds. To this aim, we generated and phenotypically characterized human SMA type 1 central nervous system (CNS) organoids derived from multiple donors. Single-cell transcriptomics analyses revealed a pervasive transcriptional alteration in multiple cell populations, beyond motor neurons, including neural progenitors. Functional analyses showed consistent defects in SMA brain and spinal organoids activity, supporting a model of widespread pathogenesis in the SMA central nervous system.We also tested newly developed peptide-conjugated antisense oligonucleotides targeting SMN expression levels at the early stages of organoid development. Results showed that the treatment can rescue morphological and functional deficits in SMA spinal cord organoids.Our molecular, morphological, and functional findings demonstrate the early-onset and pervasive developmental nature of SMA pathogenesis, which needs to be considered in the therapeutic perspectives, and provide evidence that SMA organoids represent a reliable model to explore drug kinetics and efficacy.

**Disclosures: P. Rinchetti:** None. **I. Faravelli:** None. **M. Tambalo:** None. **I. Simutin:** None. **S. Mancinelli:** None. **L. Mapelli:** None. **M. Miotto:** None. **A. D'Angelo:** None. **M. Rizzuti:**

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**Poster**

**PSTR017. Other Motor Neuron Diseases: SMA, SBMA, and Childhood ALS**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR017.08/K10

**Topic:** C.06. Neuromuscular Diseases

**Support:** NIH IRP ZIA-HD008966

**Title:** Precision mouse models of childhood ALS caused by excessive sphingolipid synthesis

**Authors: *Z. E. PICCUS**[1,2], K. GABLE[3], A. SANTOKI[1], P. MOHASSEL[4], G. LEE[5], L. HAO[5], C. BÖNNEMANN[1], T. DUNN[3], C. E. LE PICHON[1];
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**Abstract:** Amyotrophic lateral sclerosis (ALS) is a fatal disease affecting motor neurons. Recently, patients were identified with de novo mutations in the gene SPTLC1, leading to an ALS onset as early as 3 years of age. SPTLC1 is a subunit of serine palmitoyltransferase (SPT), the rate-limiting enzyme of sphingolipid (SL) synthesis. SLs are an essential lipid class which are particularly abundant in myelin and enriched in the nervous system. The ALS-linked mutations occur within a transmembrane domain (TMD) of SPT required for its negative regulation; structural data predict these mutations cause unrestrained SL synthesis. These are the first metabolic mutations linked to ALS; no previous animal models of this syndrome existed. We hypothesized that mice expressing ALS-mutant Sptlc1 will would produce excessive SLs and exhibit neurodegeneration.
Mouse and human protein sequences are highly conserved in the affected TMD, making precision mouse modeling ideal to investigate consequences of these mutations. We generated mice with the A20S disease-linked mutations in the endogenous locus to examine neurodegeneration and SL production. SLs are elevated in mutant tissues, especially in homozygotes. Both A20S animals exhibit signs of neurodegeneration revealed by thin myelination and increased levels of neurofilament light chain, a protein that accumulates in serum following axonal breakdown. Mutants exhibit progressive age-related neurodegeneration. By 1 year, A20S animals show TDP-43 mislocalization, a defining pathological feature of human ALS rarely observed in mouse models. These mice provide a preclinical model to test therapies for patients with Sptlc1 ALS-linked mutations and can be leveraged to study how high SL levels lead to neurodegeneration.

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**Poster**

**PSTR017. Other Motor Neuron Diseases: SMA, SBMA, and Childhood ALS**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR017.09/L1

**Topic:** C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

**Support:** Postdoctoral research fellow funded by Neuroscience Dept. “Rita Levi Montalcini”, University of Turin, for the project “The GABA-Mitochondria axis in Spinal Muscular Atrophy”

**Title:** GABA signalling and metabolism (dys)regulation in Spinal Muscular Atrophy: investigations in SMAΔ7 mice sensorimotor cortex"

**Authors: *G. MENDUTI**, G. BELTRANDO, A. VERCELLI, M. BOIDO;
Dept. of Neurosci. “Rita Levi Montalcini”, Neurosci. Inst. Cavalieri Ottolenghi, Univ. of Turin, Orbassano (TO), Turin, Italy

**Abstract:** Spinal muscular atrophy (SMA) is a neurodegenerative disease due to the lack of Survival Motor Neuron (SMN) protein: SMA is characterized by lower MN degeneration (MND) and muscle atrophy. However, we also observed a selective degeneration of motor cortex (CRTX) layer V pyramidal neurons in SMAΔ7 mice (a severe SMA murine model), compared to WT controls. Even if SMA genetic causes are well known, many aspects of its pathogenesis remain unclear and the available therapies still show many limits. Intriguingly, neuroprotective effects of GABA-targeting drugs were reported in SMA, suggesting a possible dysregulation of GABA and inhibitory interneuron (IN) pathways at CRTX level, as a common etiology shared with other neuronal diseases. Indeed, we have strong preliminary results showing perturbation of GABA metabolism and Parvalbumin (PV) INs functions in SMAΔ7 mice sensorimotor (SM) CRTX, in the late disease stage (postnatal day 12), in comparison with WT. By immunofluorescence (IF), we observed a significant reduction of GABAergic signal (-57%, $p<0.01$) and reduced density of GABA+-cells (-25%, $p<0.01$) in SMAΔ7 SM CRTX, along with an impaired distribution and reduction of GAD65 and GAD67 (GABA synthesis enzymes) signal (-60% and -65%, respectively, $p<0.05$) and GAD67+-cells (-20%, $p<0.05$), underlying neurotransmitter synthesis defects. Moreover, PV INs were found significantly reduced in number (-34%, $p<0.05$) and morphologically altered, suggesting possible failure in their inhibitory functions. Immunoblotting further confirmed a reduction in GAD65/67 protein levels in the SMAΔ7 SM CRTX (-25%, $p<0.05$). Furthermore, IF analyses in SMAΔ7 motor CRTX showed a reduction of GABAergic synapses contacting-neurons in L2/3 (-28%, $p<0.01$) and L5 (-38%, $p<0.001$), suggesting loss of GABAergic contribution to cortical excitatory/inhibitory homeostasis. Overall, the results show for the first time GABAergic dysregulations in the SM CRTX of SMA mice, possibly contributing to the SMA onset of MND. Further studies aimed at fully understanding and pharmacologically rescuing GABA pathways will pave the way for new SMA treatments.

**Disclosures:** **G. Menduti:** None. **G. Beltrando:** None. **A. Vercelli:** None. **M. Boido:** None.

**Poster**

**PSTR017. Other Motor Neuron Diseases: SMA, SBMA, and Childhood ALS**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR017.10/Web Only

**Topic:** C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

**Title:** Virtual screening of small molecule ligands for Profilin2a - a novel therapeutic approach for spinal muscular atrophy

**Authors: *S. A.P.**[1], K. NAGASUBRAMANIAN[2], S. JHA[3];
[1]Med. Nanotechnology, SASTRA Univ., Thanjavur, India; [2]Sch. of Chem. and Biotech., Sastra deemed Univ., THANJAVUR, India; [3]Biotech., SASTRA Deemed Univ., Thanjavur, India

**Abstract:** Spinal Muscular Atrophy (SMA) is an autosomal recessive neurodegenerative disorder characterized by pathological symptoms such as limited motor functions especially in children. This is caused by the degeneration of α-motor neurons at the anterior horn region of the spinal cord. Primary cause of SMA is deletion in the Survival Motor Neuron 1 (SMN1) gene which leads to reduced level of SMN protein. SMN is involved in actin dynamics by sequestrating profilin2a (PFN2). In the absence of SMN, hyper activity of PFN2 is observed, which is a major pathology of SMA. Hence, PFN2 is a potential target to regulate SMA pathophysiology. This study aimed to target PFN2 by in-*silico* small molecule screening. Crystal structure of PFN2 (PDB ID: 1D1J) was obtained and loops were modified using ModBase tool. The quality was then assessed by ERRAT value and was subjected to molecular docking with two ligand libraries (ZINC synthetic and Chemdiv natural small molecule library) using Schrödinger Maestro ((Schrödinger release 2022-1: GLIDE, Schrödinger, LLC, New York, NY, 2021) and subsequently ADME properties using Quikprop (Schrödinger release 2022-1: Quikprop, Schrödinger, LLC, New York, NY, 2021) was performed for selected molecules. The ERRAT score of the refined crystal structure was found to be 99.413 which was then subjected to docking using GLIDE module of Schrödinger Maestro. Natural ligand N-({1-[3-(4-fluorophenyl)-1H-pyrazol-5-yl]piperidin-4-yl}methyl)-1H-indo le-3-carboxamide and synthetic ligands ZINC000076125568 and ZINC000071927976 showed notable binding with PFN2 with minimum glide score of -5.838, -8.648 and -8.883 KCal/Mol respectively. Their interaction residues overlap with those of SMN. Results from ADME properties suggests that the natural molecule N-({1-[3-(4-fluorophenyl)-1H-pyrazol-5-yl]piperidin-4-yl}methyl)-1H-indo le-3-carboxamide has high GI absorption of 85.3%, whereas the synthetic ligands has very poor or no GI absorption. All the three ligands does not violate the Lipinski's rule of 5. Though the ligands show poor ADME properties, they could act as a potential therapeutic molecule for the treatment of SMA. In conclusion, our results suggests that three molecules, N-({1-[3-(4-fluorophenyl)-1H-pyrazol-5-yl]piperidin-4-yl}methyl)-1H-indole-3-carboxamide, ZINC000071927976 and ZINC000076125568 act as potential ligands of interest for the treatment of spinal muscular

atrophy. However, further *in-vitro* and *in-vivo* analysis is required for the optimization and potential use of these ligands for treatment of SMA.

**Disclosures: S. A.p.:** None. **K. Nagasubramanian:** None. **S. Jha:** None.

**Poster**

**PSTR017. Other Motor Neuron Diseases: SMA, SBMA, and Childhood ALS**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR017.11/L2

**Topic:** C.06. Neuromuscular Diseases

**Title:** Molecular basis of motor neuron degeneration in SCYL1 deficiency syndrome

**Authors: *A. CASSIDY**[1], E. KULIYEV[2], S. BARE[1], D. THOMAS[1], H. CHEN[1], S. GINGRAS[3], S. PELLETIER[1];
[1]Indiana Univ. Sch. of Med., Indianapolis, IN; [2]St. Jude Children's Res. Hosp., Memphis, TN; [3]Univ. of Pittsburgh, Pittsburgh, PA

**Abstract:** SCYL1 is a multidomain protein thought to regulate several essential cellular functions including membrane protein trafficking, nucleocytoplasmic shuttling of tRNAs, and transcription via interactions with several molecular complexes. In both humans and mice, inactivating *SCYL1* mutations cause a multisystem disorder characterized by recurrent episodes of liver failure, growth retardation and progressive motor dysfunction resulting from the loss of spinal motor neurons. However, the molecular mechanisms underlying this syndrome has remained elusive. Here we report the characterization of an allelic series of *Scyl1* separation-of-function mutations in mice and show that although defective protein trafficking and faulty transcription were viewed as major disease mechanism, mice harboring mutations in *Scyl1* that prevented interaction between SCYL1 and various factors involved in protein trafficking or DNA binding showed no overt abnormalities. Importantly, however, mice expressing mutant forms of SCYL1 that prevented the ability of SCYL1 to oligomerize, interact with specific membrane phospholipids or perturb its subcellular localization along the secretory pathway exhibited loss-of-function phenotypes. Together, these findings indicate that defective lipid trafficking and/or metabolism may represent a major disease mechanism in SCYL1 deficiency syndrome. Ongoing omics studies have begun to illuminate metabolic pathways deregulated in *Scyl1*-deficient mouse tissues.

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**Poster**

**PSTR018. Mechanisms of Neurotoxicity I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR018.01/L3

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH Grant DA051450

**Title:** Chronic methamphetamine administration increased mitochondrial density in substantia nigra pars compacta dopamine neurons

**Authors: *A. BHOWMIK**[1], S. M. GRAVES[2];
[1]Dept. of Pharmacol., Univ. of Minnesota, Twin Cities, Minneapolis, MN; [2]Dept. of Pharmacol., Univ. of Minnesota Twin Cities, MINNEAPOLIS, MN

**Abstract:** Methamphetamine (meth) is a highly addictive psychostimulant, and its rates of abuse in the US have increased in recent years (NSDUH 2021). In addition to being addictive, meth is also neurotoxic. Chronic (28-day) *in vivo* meth (5 mg/kg) administration results in the degeneration of substantia nigra pars compacta (SNc) dopamine neurons in male mice, which is associated with meth-induced mitochondrial oxidant stress (Graves *et al., Nat Neurosci* 23(1):15-20, 2020; Du *et al., Neuropharmacol* 200:108817, 2021; Graves *et al., Neurobiol Dis* 156:105409, 2021). The consequence of chronic *in vivo* meth administration on mitochondria in the SNc is unclear. Existing literature shows that an acute meth binge decreases parkin expression and 26S proteasome-ubiquitin activity, suggesting a deficit in mitophagy (Moszczynska *et al., J Neurochem* 116(6):1005-17, 2011). We, therefore, hypothesize that chronic meth administration will increase mitochondrial density in SNc neurons. To test this hypothesis, male C57BL/6J mice (approximately 8 weeks of age) were administered saline (10 ml/kg; i.p.; n=4 mice) or meth (5 mg/kg; i.p. n=4 mice) for 28 consecutive days, after which mice were sacrificed; brains were fixed using 4% paraformaldehyde and sectioned (40 µm). Brain slices throughout the SNc were collected, and every sixth section was stained for tyrosine hydroxylase (TH) to label dopamine neurons. Slices were counterstained for the voltage-dependent anion-selective channel protein 1 (VDAC1) to label mitochondria. High-resolution *z*-stacks (0.101 µm x 0.101 µm; 0.3 µm steps), entailing the soma of SNc neurons, were acquired using an Apotome fluorescence microscope (Zeiss). Imaris MeasurementPro software was used to generate 3D reconstructions of the soma of SNc neurons and estimates of mitochondrial density calculated as the volume occupied by mitochondria (VDAC1 staining) in the somatic compartment divided by the total somatic volume (TH staining) using the surface object function; 14-20 neurons were collected per mouse per group and data analyzed using a nested *t*-test. Chronic meth administration increased mitochondrial density in the soma of SNc ($p<0.0001$) neurons in male mice (saline: n= 66 neurons/4 mice; meth: n= 70 neurons/4 mice). Further study is needed to determine whether chronic meth similarly impacts SNc mitochondrial density in female subjects.

**Disclosures: A. Bhowmik:** None. **S.M. Graves:** None.

**Poster**

**PSTR018. Mechanisms of Neurotoxicity I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR018.02/L4

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH Grant DA054779
NIH Grant DA051450

**Title:** Chronic methamphetamine administration produces axonal loss prior to somatic loss of substantia nigra pars compacta and locus coeruleus neurons in male mice

**Authors: *A. PILSKI**[1], S. M. GRAVES[2];
[1]Pharmacol., Univ. of Minnesota Twin Cities, Minneapolis, MN; [2]Pharmacol., Univ. of Minnesota Twin Cities, MINNEAPOLIS, MN

**Abstract:** Methamphetamine (meth) is an addictive stimulant with neurotoxic effects. In substantia nigra pars compacta (SNc) dopamine neurons meth increases axonal but not somatic mitochondrial oxidant stress and this meth-induced mitochondrial oxidant stress is prevented by monoamine oxidase (MAO) inhibition (Graves *et al*., *Nat Neurosci* 23(1):15-20, 2020; Du *et al., Neuropharmacology* 1;200:108817, 2021). Similarly, meth increases MAO-dependent mitochondrial oxidant stress in axons of locus coeruleus (LC) noradrenergic neurons (Du *et al., Front Cell Neurosci* 16:949923, 2022). Chronic (28 day) *in vivo* administration of meth (5 mg/kg) results in degeneration of both SNc (Du *et al., Neuropharmacology* 1;200:108817, 2021; Graves *et al., Neurobiol Dis* 156:105409, 2021) and LC neurons (Du *et al., Front Cell Neurosci* 16:949923, 2022) which is also prevented by MAO inhibition, suggesting that the degenerative process starts in the axonal compartment. We therefore hypothesized that chronic meth administration would result in axon loss prior to somatic loss in SNc and LC neurons. To test this hypothesis, male C57BL/6J mice (~8 weeks old) were administered saline or meth (5 mg/kg; i.p.) for 14, 21, or 28 days and brain sections (40 µm) entailing the SNc and dorsolateral striatum (DLS) as well as sections entailing the LC and motor cortex collected. SNc dopamine neurons and axons in the DLS were stained for tyrosine hydroxylase ($TH^+$). LC noradrenergic neurons were stained for $TH^+$ and LC axons in the motor cortex for the norepinephrine transporter ($NET^+$). The number of $TH^+$ neurons in the SNc and LC and $TH^+$ and $NET^+$ axon length in the DLS and motor cortex, respectively, were stereologically quantified by a blinded experimenter; data analyzed using unpaired *t*-tests (n=6 mice/group). In male mice 14- ($p=0.0012$) and 21-day ($p=0.0043$) meth treatment resulted in decreased $TH^+$ axon length in the DLS without somatic loss in the SNc, whereas 28-day meth resulted in axonal ($p=0.0050$) and somatic ($p=0.0092$) loss. Similarly, 14- ($p=0.0131$) and 21-day ($p=0.0010$) meth treatment resulted in decreased $NET^+$ axon length in the motor cortex without somatic loss in the LC, whereas 28-day meth resulted in both axonal ($p<0.0001$) and somatic ($p=0.0002$) loss. Presented data suggest that chronic meth causes a progressive dying-back pattern consistent with that observed in the SNc (Kordower *et al., Brain* 136(8):2419-2431, 2013) and LC (Doppler *et al., Brain* 144(9):2732-2744, 2021) in patients with Parkinson's disease, a progressive neurodegenerative disorder for which people with a history of meth abuse are at increased risk (Curtin *et al., Drug Alcohol Depend* 146:30-8, 2015).

**Disclosures:** **A. Pilski:** None. **S.M. Graves:** None.

**Poster**

**PSTR018. Mechanisms of Neurotoxicity I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR018.03/L5

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH grant DA051450
NIH grant AG070962
NIH grant DA054779

**Title:** Protracted abstinence from chronic methamphetamine administration decreases the number of tyrosine hydroxylase-stained neurons in the substantia nigra pars compacta and locus coeruleus in female mice

**Authors: L. BOATNER**[1], A. BHOWMIK[2], A. PILSKI[3], *S. GRAVES[4];
[1]Pharmacol., Univ. of Minnesota - Twin Cities, Minneapolis, MN; [2]Univ. of Minnesota, Twin Cities, Minneapolis, MN; [3]Univ. of Minnesota Twin Cities, Minneapolis, MN; [4]Pharmacol., Univ. of Minnesota Twin Cities, MINNEAPOLIS, MN

**Abstract:** Methamphetamine (meth) is an addictive and neurotoxic psychostimulant. Our lab has previously shown that chronic 28-day administration of meth (5 mg/kg) results in degeneration of substantia nigra pars compacta (SNc) dopamine (Du *et al., Neuropharmacology* 200:108817, 2021) and locus coeruleus (LC) norepinephrine neurons in male mice (Du *et al., Front Cell Neurosci* 16:949923, 2022). Female mice are resistant to nigrostriatal neurotoxicity induced by an acute binge administration of meth (Dluzen *et al*., *Ann. N.Y. Acad. Sci.* 1074:282-294, 2006); whether female mice are similarly resistant to chronic meth-induced degeneration of SNc and LC neurons is unclear. To determine the consequence of chronic meth on SNc and LC neurons in female mice, adult female C57BL/6J mice (approximately 8 weeks of age) were administered saline or meth (5 mg/kg) intraperitoneally for 28 days after which brains were harvested, tissue sectioned, and immunostained for tyrosine hydroxylase ($TH^+$) as in prior studies (Du *et al., Neuropharmacology* 200:108817, 2021; Du *et al., Front Cell Neurosci* 16:949923, 2022). The number of $TH^+$ SNc and LC neurons were stereologically quantified by a blinded experimenter. In contrast to previous results in male subjects (Du *et al., Neuropharmacology* 200:108817, 2021; Du *et al., Front Cell Neurosci* 16:949923, 2022), chronic 28-day meth administration had no effect on the number of $TH^+$ neurons in the SNc ($p=0.7397$) or LC ($p=0.8692$) in female mice; n=6 mice/group. In male rats trained to self-administer meth (Kousik *et al., Eur J Neurosci* 40:2707, 2014) and male mice administered a sub-chronic regimen of meth (Graves *et al., Neurobiol Dis* 156:105409, 2021), degeneration becomes apparent after a period of abstinence. To determine whether female subjects remain resistant to degeneration during abstinence, female mice were treated with saline or meth (5 mg/kg; IP) for 28 days and sacrificed after 56-days of abstinence. Brains were harvested, sectioned, stained and the number of $TH^+$ SNc and LC

neurons stereologically quantified by a blinded experimenter. The number of $TH^+$ neurons in the SNc ($p<0.0001$) and LC ($p=0.0033$) were decreased after protracted abstinence from chronic meth administration. Saline and meth treated groups were compared and analyzed using unpaired *t*-tests; n=6 mice/group. Current results indicate that, while female mice show resistance to the deleterious effects of chronic meth, degeneration does appear to emerge after a period of abstinence.

**Disclosures: L. Boatner:** None. **A. Bhowmik:** None. **A. Pilski:** None. **S. Graves:** None.

**Poster**

**PSTR018. Mechanisms of Neurotoxicity I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR018.04/L6

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** I01 BX003431/BX/BLRD VA/United States
U01 MH092758/MH/NIMH NIH HHS/United States

**Title:** Expression of PER1 Following Methamphetamine in Bipolar Disorder Patient Neural Progenitor Cells from Lithium Responders and Lithium Non-Responders

**Authors: *A. MANDYAM**[1], H. MISHRA[2], M. MCCARTHY[3];
[1]Biosci., Rice Univ., Houston, TX; [2]UCSD, San Diego, CA; [3]VA San Diego Healthcare Syst., VA San Diego Healthcare Syst., San Diego, CA

**Abstract:** Bipolar disorder (BD) is a genetically inherited mood disorder characterized by extensive disruption in circadian function. Lithium is a mood stabilizer used to treat BD, but many patients do not respond to treatment. Lithium may stabilize disruptions in circadian rhythm caused by BD and is neuroprotective. However, mechanisms underlying lithium's regulation of circadian rhythm and cell death in BD are not well understood. Studies in murine cell lines have examined the effects of lithium on expression of genes regulating circadian rhythms and report that lithium increases the expression of Period 2 (*PER2*) and decreases the expression of *PER3*. *PER1* also plays an integral role in maintaining the circadian rhythm and lithium could affect *PER1* to prolong circadian period. We have also found previously that *PER1* is also involved in regulating programmed cell death. In the current study we examined the effect of lithium on expression of *PER1* in a human neuronal model of BD using induced pluripotent stem-cell (iPSC) technology. We used neural progenitor cells (NPCs) derived from iPSCs from lithium responsive (Li-Rs) and lithium nonresponsive (Li-NRs) BD patients and age-matched control subjects. Methamphetamine (Meth) is a drug that stimulates release of the neurotransmitter dopamine and produces cell death at high concentrations. Increased dopamine release is observed in the manic phase of BD; therefore, we used Meth to model neuronal loss associated with mania and determine whether cell death and *PER1* expression differed between Li-R, Li-NR and control NPCs. NPCs from each group were incubated with Meth (1 mM), lithium (Li; 10

mM) + Meth or saline, and were processed for fluorescent immunocytochemistry to determine neurotoxicity (Image-IT DEAD) and expression of *PER1*. NPCs were imaged and quantified with ImageJ in a blinded fashion. We have recently shown that pre-treatment of NPCs with lithium before Meth reversed the neurotoxic effects of Meth in control NPCs, whereas Li-NR showed less protective benefit. Li-R cells showed decreased levels of IT-DEAD cells after Meth and comparatively high viability, and lithium treatment did not increase viability any further. We add to these findings to show that neither Meth nor pre-treatment with lithium altered *PER1* expression in NPCs from control, Li-R or Li-NR BD donors. Future studies will determine whether Meth differentially affects expression of other Period genes in Li-R and Li-NR NPCs, as lithium alters *PER2* and *PER3* to regulate circadian function. Therefore, the current in-vitro system can be further researched to investigate circadian rhythm disruptions and cell death in BD and biomarkers for lithium responsiveness.

**Disclosures: A. Mandyam:** None. **H. Mishra:** None. **M. McCarthy:** None.

**Poster**

**PSTR018. Mechanisms of Neurotoxicity I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR018.05/L7

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIADID Grant: 1 R15 AI156879
NIGMS Grant: 5P20GM103427

**Title:** Investigating the inflammatory impact of long non-coding RNA expression in aminoglycoside related cochlear ototoxicity

**Authors: *E. DAFFER**[1], C. M. JACKSON[1], A. SHIBATA[1], D. HE[2], P. STEYGER[2], C. TIAN[2]; [1]Biol., [2]Sch. of Med., Creighton Univ., Omaha, NE

**Abstract:** Ototoxicity and permanent hearing loss occur in 20-50% of patients treated with aminoglycoside antibiotics for bacterial ear infections. Inflammatory responses in the cochlea enhance the ototoxicity of aminoglycosides. The mechanism by which inflammatory responses potentiate aminoglycoside ototoxicity is not well understood. Preliminary data shows that inflammatory responses in the cochlea and brain of animal models and auditory cell lines involve the upregulation of proinflammatory long noncoding RNAs (lncRNAs). In LPS-induced endotoxemic mice, lncRNA Nostrill was significantly upregulated 2.1 ± 0.3fold. AK15331 was upregulated 2.3 ± 0.1fold and lincRNA-Cox2 and lincRNA-Tnfaip3 were upregulated 2.3 ± 0.3fold and 2.5 ± 0.4fold, respectively. Proinflammatory genes ccl2, iNos, Tnf-α, Cxcl2, Il-1β were significantly upregulated in cochlea tissue 24hr after LPS injection. Interestingly, RT-qPCR analysis of TLR4 knockout mice showed that knockout of TLR4 expression significantly reduces the upregulation of lincRNA-Tnfaip3 and lincRNA-Cox2 following LPS stimulation but does not block LPS-induced upregulation of Nostrill. LPS-induced, proinflammatory cytokine

expression was suppressed in TLR4KO mice. Genome-wide single cell expression analyses were used to identify cell types expressing upregulated and downregulated genes during the inflammatory responses. RT-qPCR and in situ were used to validate and localize differentially expressed lncRNA in the nervous system of the in vivo mouse model. Additionally, in vitro studies in auditory cell lines are currently underway to investigate the mechanisms by which lincRNAs regulate endotoxemia and increased aminoglycoside-associated ototoxicity.

**Disclosures:** **E. Daffer:** None. **C.M. Jackson:** None. **A. Shibata:** None. **D. He:** None. **P. Steyger:** None. **C. Tian:** None.

**Poster**

**PSTR018. Mechanisms of Neurotoxicity I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR018.06/L8

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** University of the Witwatersrand, Faculty of Health Sciences Faculty Research Committee Individual Grant awarded to Jaclyn Asouzu Johnson in 2019 and 2021 (grant number; 00125484211015121105000000000000005254)

**Title:** Neuroplasticity perturbations and atrophy in the frontal lobe and cerebellum of alcohol treated diabetic male Sprague Dawley rats

**Authors: *J. E. ASOUZU JOHNSON**, E. MBAJIORGU;
Anatom. Sci., Univ. of the Witwatersrand, Johannesburg, South Africa

**Abstract:** Alcohol consumption is prevalent in sub-Saharan Africa and globally with associated harmful effects on the central nervous system. Alcohol use is further associated with metabolic deficits contributing to the pathogenesis of Type 2 Diabetes (T2D). Diabetes and alcohol are independently reported to induce neuroplasticity deficits and apoptosis in several brain regions resulting in dementia and cognitive deficits. While some alcohol-induced neurobehavioral effects are considered reversible with sobriety, the molecular and resulting structural perturbation of alcohol in a diabetic state remains unclear. Therefore, this study aims to investigate the concomitant effect of alcohol in a diabetic state on the cortical size, white matter profile, and mRNA levels of plasticity proteins in the frontal lobe and cerebellum. Male Sprague Dawley rats were divided into 4 groups of six rats each including, NC (untreated groups), AL (normal rats treated with 10% ethanol), DB (diabetic rats), and DAL (diabetic rats treated with 10% ethanol). After ninety days of treatment, the rats were terminated, the brains were excised for, quantitative PCR of apoptosis (caspase-3, BAX, and BCL2) and plasticity (DLG4, mTOR, and synaptophysin) mRNA levels, and Nissl and Luxol Fast Blue stains for histomorphology analysis of cortical volume and myelin profile of white matter tracts respectively. Our results show that AL reduced cortical thickness, and white matter tracts in the frontal lobe and cerebellum, while

DB significantly impacted all the parameters investigated. However, DAL significantly reduces cortical thickness and white matter tracts despite elevated caspase-3, BAX, and BCL2 and downregulated DLG4, mTOR, and synaptophysin in the frontal lobe and cerebellum. These findings indicate that alcohol use in diabetes may induce some antiapoptotic response amid exacerbated apoptosis, with declining cortical histomorphology and neuroplasticity that may adversely impact neurological health.

**Disclosures: J.E. Asouzu Johnson:** None. **E. Mbajiorgu:** None.

**Poster**

**PSTR018. Mechanisms of Neurotoxicity I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR018.07/M1

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** Rhode Island Medical Research Foundation
Roddy Foundation
College of Pharmacy, University of Rhode Island
George and Anne Ryan Institute for Neuroscience, University of Rhode Island

**Title:** Interplay between microplastic exposure and age-related cognitive decline

**Authors: *L. GASPAR**, S. BARTMAN, G. COPPOTELLI, J. M. ROSS;
George and Anne Ryan Inst. for Neuroscience; 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 at the smallest end of the microplastics spectrum. 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 both *in vitro* and *in vivo* models. At the cellular level, viability assays using U-2 OS cells showed decreased cell survival following exposure to PS-MPs and fluorescence imaging revealed perinuclear accumulation of MPs. These adverse outcomes prompted further investigation at a higher level. Following a three-week exposure to fluorescently-labeled PS-MPs via drinking water, young (4

months) and old (21 months) female C57/BL6J mice were assessed using behavioral assays, such as open-field and light/dark preference, followed by tissue analyses, using Western blot, qPCR, and immunohistochemistry. These analyses revealed detectable MPs in each tissue examined, including brain. Data from these assays additionally suggests that short-term exposure to MPs induced striking neurobehavioral changes as well as alterations of immune markers in liver and brain, with changes appearing to occur in an age-dependent manner. These findings suggest the need for further research to better understand the mechanisms by which microplastics may induce physiological and cognitive alterations.

**Disclosures:** **L. Gaspar:** None. **S. Bartman:** None. **G. Coppotelli:** None. **J.M. Ross:** None.

**Poster**

**PSTR018. Mechanisms of Neurotoxicity I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR018.08/M2

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH Grant R01553717

**Title:** Wildfire smoke and ozone induced metabolic and neuroinflammatory outcomes mediated by the interplay of dietary fatty acids

**Authors:** ***B. E. BAIRD**[1], R. HUNTER[1], J. R. CARTER[2], E. BARR[1], J. BEGAY[1], G. HERBERT[1], S. LUCAS[1], Y. JIN[3], H. GU[3], S. NOOR[2], M. CAMPEN[1];
[1]Pharmaceut. Sci., [2]Neurobio., Univ. of New Mexico, Albuquerque, NM; [3]Intrnl. Med., Florida Intl. Univ., Pt. St. Lucie, FL

**Abstract:** Deteriorated air quality is one of several critical pathways through which climate change may have large-scale impacts on human health. Wildfires across the United States have steadily increased over the past 40 years, largely as a result of climate change. Smoke from wildfires can cause a number of cardiovascular and respiratory diseases, with new studies highlighting potential neurological outcomes. Ozone, produced by the reaction of sunlight with gaseous precursors, is another climate change-related pollutant that can cause similar extrapulmonary outcomes. Factors that modulate the neurological effects of these inhaled toxicants remain largely unstudied. To address the impact of dietary factors, we introduced supplemented standard chow enriched with saturated and polyunsaturated fats (PUFAs) in order to investigate how different fatty acids may impact neuroinflammation acutely following air pollution exposure. Fatty acid diet types included coconut oil (saturated fat) soybean oil, (PUFA, Omega-6), flaxseed oil (PUFA, Omega-3) and a standard grain chow. 24 hours after a single 4-h air pollution exposure, brain tissue was collected for lipidomics, metabolomics, and gene expression assays. Primary mouse brain endothelial cells were treated with serum from exposed or control mice and assayed for barrier integrity evaluation using electric cell-substrate impedance sensing (ECIS). Metabolite profiles within the brain changed with both ozone

inhalation and diet type. The coconut oil diet significantly decreased levels of serotonin within the brain. Phenylalanine and kynurenine levels also demonstrated diet and exposure dependent changes towards a more health-adverse phenotype. Gene expression data demonstrated higher levels of claudin 5 within the brain with ozone exposure. This potentially indicates a protective compensatory mechanism in response to a toxic interaction at the blood-brain barrier. Both the gene expression and ECIS data demonstrate the ability of diet to impact cellular integrity and interact with the adverse neurological outcomes of ozone inhalation. Primary endothelial cells treated with the supplemented diet serum demonstrated higher resistance between cells, indicating tighter junctions, but little impact of the ozone exposure.These data highlight the critical roles of dietary lipids in modulating the neurometabolic outcomes of inhaled pollutants; further research detailing the mitigation of toxicity could lead to public health-based recommendations following air pollution events.

**Disclosures:** **B.E. Baird:** None. **R. Hunter:** None. **J.R. Carter:** None. **E. Barr:** None. **J. Begay:** None. **G. Herbert:** None. **S. Lucas:** None. **Y. Jin:** None. **H. Gu:** None. **S. Noor:** None. **M. Campen:** None.

**Poster**

**PSTR018. Mechanisms of Neurotoxicity I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR018.09/M3

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** National Institute on Aging Grant R01-AG070776

**Title:** Inhaled Wildfire Smoke Particulate Drives Aberrant Proteinopathy-related Changes in the Adult Mouse Brain

**Authors: *M. K. SIDDIQI**[1], J. M. GONZALES[1], C. G. CANAL[1], D. P. SCIESZKA[1], M. J. CAMPEN[2], A. K. OTTENS[1];
[1]Anat. and Neurobio., Virginia Commonwealth Univ., Richmond, VA; [2]Pharmaceut. Sci., Univ. of New Mexico, Albuquerque, NM

**Abstract:** An increasing frequency and intensity of wildfires represents a significant public health concern and is expected to cause an annual U.S. mortality of >40,000 by the end of the 21st century. Wildfire smoke (WFS) releases a high concentration of $PM_{2.5}$ ($\leq$ 2.5 μm particulate matter) that spreads widely in the atmosphere and creates an unhealthy, toxic atmosphere over long distances. Respiratory complaints from WFS are very common and hospitalizations due to cardiovascular morbidities also increase in areas impacted by WFS; however, impacts to brain health and particularly neurodegenerative disease pathogenesis remains poorly understood. $PM_{2.5}$ from engine combustion sources has shown an alarming increased risk for neurodegenerative and other neurological outcomes, raising the concern of a similar burden with WFS. To address this gap, this study employed an unbiased neuroproteomic investigation into the pathobiological

outcomes following 3-weeks of 4h/day exposure to inhaled real-world WFS particulate (100 µg/$m^3$). Focus was placed on the hippocampus, a key region of pathogenesis in Alzheimer's Disease and related dementias. Of 2,649 unique proteins assessed, 785 were significantly responsive to WFS in terms of their abundance, post-translational modifications, and distribution between cytosolic and membranous cellular compartments. Enrichment analysis showed strong associations with neurodegenerative disease pathways for Alzheimer's and Parkinson's, with >20% of protein findings connected. Notably, aggregating proteins tau, amyloid and synuclein associated with neurodegeneration were all increased two-fold or greater and shifted in their localization in the cell, supporting their aberrant accumulation in accord with disease pathogenesis. Hyperphosphorylated tau was evident by microscopy broadly across the hippocampus, while amyloid pathology was evident more localized, particularly in the granular layer for amyloid protein accumulation and the molecular layer for Aβ-42 peptide. Further pathway analysis indicated an increase in autophagy, specifically enriched in association with aggrephagy (FDR $3.5e^{-6}$), the selective phagocytosis and degradation of aggregated protein. Reduced levels of beta-catenin further supported an auto-feedback maintenance of autophagic activity. Together, this study provides new insights into the relationship between WFS and pathogenesis of neurodegenerative disease relevant proteinopathy and underscores the need to understand longer-term health implications and development of suitable interventions to protect against WFS exposure.

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**Poster**

**PSTR018. Mechanisms of Neurotoxicity I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR018.10/M4

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** R01NS117906

**Title:** Metformin Ameliorates Neuroinflammation In Primary Neuron-Astrocyte & Adolescent Mice Induced By Tobacco Smoke : Role Of Nrf2 Activation

**Authors: *K. AKTER**[1], S. SHARMA[2], S. RAHMAN ARCHIE[3], Z. YONG[4], T. J ABBRUSCATO[2];
[1]Pharmaceut. Sci., Texas Tech. Univ., Amarillo, TX; [2]Pharmaceut. Sci., [3]Texas Tech. Univ. Hlth. Sci. Ctr., [4]Texas Tech. Univ. Hlth. Sci. Ctr., Amarillo, TX

**Abstract: Metformin ameliorates neuroinflammatory environment for neurons and astrocytes during in-vitro and in-vivo stroke and tobacco smoke chemical exposure: Role of Nrf2 activation Authors *KA. AKTER[1]**, S. SHARMA[1], SR. ARCHIE[1], Y. ZHANG[1], TJ. ABBRUSCATO[1]; [1]Department of Pharmaceutical Sciences, School of Pharmacy, Texas Tech

University Health Sciences Center, Amarillo, TX 79106, USA**DisclosuresKA. Akter**: None. **S. Sharma**: None. **SR. Archie**: None. **Y. Zhang**: None. **TJ. Abbruscato**: None**Abstract**Despite the protective nature of the blood-brain barrier and brain-protecting tissues, some types of CNS injury, or stress can cause cerebral cytokine production and profound alterations in brain function. Neuroinflammation, which can also be accompanied by increased cerebral cytokine production, has a significant impact on the pathogenesis of many neurological illnesses, including loss of BBB integrity and ischemic stroke, yet effective treatment choices are currently lacking. Although little is known about metformin (MF), a commonly prescribed first line antidiabetic drug, prior research suggested that it may be useful in preventing BBB deterioration and the increased risk of stroke caused by tobacco smoking (TS). Therefore, reducing neuroinflammation by increasing anti-inflammatory cytokine production and decreasing pro-inflammatory cytokine production is an effective therapeutic goal for ischemic stroke. Hence, the present study was designed to explore the potential role of MF against stroke and TS induced neuroinflammation and ROS production in vitro and in vivo. Our studies revealed that, MF suppressed the release of pro-inflammatory mediators like tumor necrosis factor-α, interleukin-1β by targeting nuclear factor kappa B (NF-κB) signaling pathway in primary astrocytes and neuron. MF also upregulated anti-inflammatory mediators, such as interleukin-10, interleukin-4 by the upregulation of Nrf2-ARE signaling pathway. Adolescent mice receiving MF along with TS also showed significant decrease in NF-κB expression compared to the mice not treated with MF and significantly decreased the level of TNF-α, IL-1β, MCP-1 and MIP-2 and increased the level of IL-10 and IL-4 through the activation of Nrf2-ARE pathway. These results suggest that MF has anti-neuroinflammatory effects via inhibition of NF-κB signaling through the activation of Nrf2-ARE. These studies support that MF could be an excellent candidate drug for the treatment and or prevention of tobacco smoke induced neuroinflammation and ischemic stroke. Future studies will test the effects of nicotine exposure from e-Cig exposure. The work was supported by R01NS117906.

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**Poster**

**PSTR018. Mechanisms of Neurotoxicity I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR018.11/M5

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** VA Merit Award 101 BX004161-01
NIH R01 ES028104
NIH R01 AG076142
NIH R01 AG077826
NIH R01 ES029835

**Title:** Trem2 regulates ozone-induced immune cell trafficking and neuroinflammation in the lung-brain axis

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**Abstract:** Alzheimer's disease (AD) is the leading cause of dementia, and reports implicate a potential role for disrupted immune cell trafficking in the disease. Evidence supports that environmental factors play a role in AD etiology, and epidemiology reports have linked ozone ($O_3$) exposure to increased AD incidence. $O_3$ is a reactive oxidant that is confined to the respiratory tract after inhalation and is unable to translocate to the brain, highlighting a potential role for the pulmonary immune response in central nervous system (CNS) effects (The Lung-Brain Axis). Recently, genome-wide association studies have identified loss of function *Trem2* (Triggering Receptor Expressed on Myeloid Cells 2) mutations, indicating myeloid cell-specific mutations can convey AD risk. We have previously shown $O_3$ disrupts the chemotactic microglial response to amyloid plaques and disturbs the disease-associated microglia phenotype in 5xFAD mice. These are processes regulated by TREM2, supporting a role for TREM2 in the CNS effects of $O_3$. However, the role of TREM2 in the lung-brain axis has yet to be directly tested, and whether TREM2 regulates the $O_3$-induced peripheral immune mechanisms that could impact the brain is unknown. To begin to address these questions, male *Trem2*$^{-/-}$ mice and *Trem2*$^{+/+}$ control mice were exposed to either filtered air, 1 ppm $O_3$ or 2 ppm $O_3$, and bronchoalveolar lavage fluid (BALF), plasma, cervical lymph nodes (deep and lateral, CLNs), and brains were collected. Data revealed 2 ppm $O_3$ exposure caused an increase in the percent of neutrophils in the BALF of *Trem2*$^{-/-}$ mice compared to *Trem2*$^{+/+}$ mice. *Trem2*$^{-/-}$ mice also showed transcriptional changes indicative of modified neuroinflammatory response in the cortex and midbrain. In cortex and midbrain, *Tnf* expression trended higher in 2 ppm $O_3$-exposed *Trem2*$^{+/+}$ mice compared to filtered air controls, but *Tnf* expression remained unchanged in *Trem2*$^{-/-}$ mice after $O_3$ exposure. Quantitative analysis of midbrain cDNA showed a genotype-exposure interaction in *Il-1β* and *Nlrp3* expression. CLN transcriptional changes were analyzed and revealed that 1 ppm and 2 ppm $O_3$ exposures changed gene expression patterns indicative of modified immune cell trafficking, which was dependent upon *Trem2* genotype. For example, *Trem2*$^{-/-}$ mice exposed to $O_3$ showed changes in gene expression patterns indicative of an increase in T-cells, which did not occur in *Trem2*$^{+/+}$ mice. Collectively, these findings indicate that TREM2 regulates $O_3$-induced immune cell trafficking as well as neuroinflammation in the lung-brain axis, illustrating TREM2's impact in the periphery may very well affect the CNS neuroimmune milieu and regulate CNS health and disease.

**Disclosures:** **J. Malley:** None. **H. Greve:** None. **A. Tsoggerel:** None. **C. Ahmed:** None. **G. Chittum:** None. **M.T. Gomez Ponce:** None. **J.A. Johnson:** None. **L. Miller:** None. **W. Woodward:** None. **M.L. Block:** None.

**Poster**

**PSTR018. Mechanisms of Neurotoxicity I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR018.12/M7

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH Grant ES031656

**Title:** Epigenetic response to neurotoxic effects of organophosphates in a mouse model of Gulf War illness

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**Abstract:** In 1991, the USA and allies sent nearly one million troops to the Persian Gulf in the first Gulf War. Among the troops who participated in the conflict, between 25 and 35 percent became ill with a multi-symptom and often debilitating malaise now termed Gulf War illness (GWI). Many of those afflicted show symptoms 32 years after termination of the conflict and the cause and persistence of GWI remain unknown. Animal models have been developed to mimic the exposures experienced by the troops and among the many exposures proposed, one promising exposure scenario is exposure to organophosphate compounds (OP) - including sarin nerve gas- coupled with high circulating glucocorticoids. The exposure regimen leads to enhanced neuroinflammatory response to the inflammagens. The endpoint indicative measures include increased expression of pro-inflammatory cytokine genes, particularly *Il1b*. In addressing the chronic nature of the disease, we performed an experiment to identify genes whose expression has been altered by DNA methylation in our animal model. We exposed male and female C57BL/6J (B6) and DBA/2J (D2) mice to corticosterone in their drinking water for one week followed by injection of diisopropyl fluorophosphate (DFP), a sarin surrogate, at 4 mg $kg^{-1}$ i.p. Control animals received normal husbandry only. Twelve weeks later, we harvested the medial prefrontal cortex for methylome analysis by whole genome MBD-seq. Overall, 68 CpG regions across the genome showed methylation changes caused by exposure or exposure by strain interaction. One strong signal was observed in an intron near the aldo-keto reductase (*Akr1c14*) gene. Methylation signals were observed near three additional genes, neuronal tubulin glutamylation (*Ttll7*), choline transporter (*Slc44a4*), and RUN and SH3 Domain Containing 2 (*Rusc2*). Moreover, the strain-by-exposure interaction showed that *Akr1c14* methylation in the B6 strain decreased with treatment, whereas it did not in D2 mice. In conclusion, we show the efficacy of this genetic approach to understanding individual differences in the epigenetic consequences of exposure to OP and consequently the chronicity of GWI.

**Disclosures: B.C. Jones:** None. **K. Mozhui:** None. **J.P. O'Callaghan:** None. **D.G. Ashbrook:** None. **P.J.C. Prins:** None. **L. Lu:** None. **W. Zhao:** None.

**Poster**

**PSTR018. Mechanisms of Neurotoxicity I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR018.13/Web Only

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Increased expression of caspases 3 and 8 and decreased BCL-2 in frontal cortex, hippocampus and cerebellum in rats exposed to ozone and subjected to the Kindling model.

**Authors: *A. PORTILLA**[1], P. RODRIGUEZ-QUINTERO[1,3], D. VÁZQUEZ[1], E. URIBE[2], C. RUBIO[1];
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**Abstract:** Increased expression of caspases 3 and 8 and decreased Bcl-2 in frontal cortex, hippocampus and cerebellum in rats exposed to ozone and subjected to the Kindling model.
Alonso Portilla[1], Paola Rodríguez-Quintero [2], David Vázquez[1], Eric Uribe[1], Carmen Rubio[1]*[1]Departamento de Neurofisiología, Instituto Nacional de Neurología y Neurocirugía "MVS" Ciudad de México. México[2]Instituto Politécnico Nacional Ciudad de México. México
***Corresponding authorCarmen Rubio, Ph.D. Instituto Nacional de Neurología y Neurocirugía, M.V.S.Departamento de Neufisiología, Insurgentes Sur 3877, Ciudad de México 14269 MéxicoPhone number: (55) 5606 3822 Ext. 1032E-mail: macaru4@yahoo.com.mxORCID: 0000-0002-4775-5043**
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**ABSTRACT Background:** Air pollution is one of the most important problem on public health, and the Ozone ($O_3$) is one of the primary air pollutants. It is formed by a photochemical reaction of volatile organic compounds (VOC), nitrogen oxides (NOx), and sunlight. According to the World Health Organization (WHO), $O_3$ levels above 100 $\mu g/m^3$ for a daily exposure time of 8 hours or more are harmful to health. $O_3$ causes oxidative stress, causing lipid oxidation, inflammation, metabolic and cell signaling changes, and possibly the onset of cell death in sensitive brain areas. It is known that inflammation and oxidative stress can induce cell death, mainly through the apoptosis pathway. Apoptosis is programmed cell death characterized by the activation of caspases, DNA fragmentation, and apoptotic bodies formation. **Objective:** This study aims to recognize the expression of the pro-apoptotic proteins and the anti-apoptotic protein Bcl-2 in an acute $O_3$ exposure context in rats' frontal cortex, cerebellum, and hippocampus. **Methods:** Twenty Wistar rats (250-300 g) were divided into two groups. For 12 hours, the control group (n=10) was exposed to polluted free air, whereas the experimental group (n=10) was exposed to 1ppm of $O_3$. After the exposure, they were sacrificed for immunofluorescence and Western blot analysis. A t-test was used for independent samples, and both groups' arbitrary units of pro-apoptotic proteins and Bcl-2 were compared. **Results and conclusions:** We found significant differences in caspase-3 and 8, Bcl-2, and TUNEL, showing that acute $O_3$ exposure can initiate the neuronal apoptotic machinary mainly through the extrinsic pathway in the hippocampus, cerebellum, and frontal cortex.
**KEYWORDS:** apoptosis, ozone, toxicity, intrinsic pathway, extrinsic pathway, oxidative stress
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**Disclosures:** **A. Portilla:** None. **P. Rodriguez-Quintero:** None. **D. Vázquez:** None. **E. Uribe:** None. **C. Rubio:** None.

**Poster**

**PSTR018. Mechanisms of Neurotoxicity I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR018.14/M8

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** PAPIIT-UNAM IN-221521 fos SRA
CONAHCYT CVU 385286 for AMM

**Title:** Effect of oxidative stress on SOD activity and NFkB intracellular distribution in substantia nigra and intestine of rats exposed to low ozone doses

**Authors: *A. MIRANDA-MARTINEZ**[1], A. RODRÍGUEZ-MARTÍNEZ[2], E. HERNÁNDEZ-OROZCO[2], M. VALDÉS-FUENTES[2], S. RIVAS-ARANCIBIA[2];
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**Abstract:** Effect of oxidative stress on SOD activity and NFkB intracellular distribution in substantia nigra and intestine of rats exposed to low ozone doses.Miranda-Martínez Alfredo, Rodríguez-Martínez Ana Erika, Hernández-Orozco Eduardo, Marlen Valdés Fuentes, Rivas-Arancibia Selva Departamento de Fisiología, Facultad de Medicina Universidad Nacional Autónoma de México CDMX, México.Abstract Environmental pollution is one of the most critical public health problems due to its relationship with chronic-degenerative diseases. It has been shown that repeated exposure to low ozone doses increases reactive oxygen species, causing a chronic state of oxidative stress. This redox imbalance is produced by the inability of antioxidant systems to counteract the reactive species. The objective of this work was to study the effect of oxidative stress on SOD activity and the intracellular distribution of NF*k*B in the jejunum, colon, and substantia nigra in rats exposed to ozone (O3). For this purpose, 36 male Wistar rats were divided into six experimental groups (n = 6). Group 1 was exposed to ozone-free air, and groups 2, 3, 4, 5, and 6 were exposed to 0.25 ppm ozone 4 hours a day for 7, 15, 30, 60, and 90 days respectively. Once the treatments were finished, the animals were deeply anesthetized (NOM-033-SAG-ZOO-2014), and the jejunum, colon, and substantia nigra were extracted. The tissues were treated for biochemical (peroxidized lipids), colorimetric (SOD activity), and immunohistochemical (intracellular distribution of NF*k*B) techniques. The results show a significant increase in oxidized lipids in the jejunum, colon, and substantia nigra from 7 to 30 days of exposure ($p < 0.05$), an increase in SOD levels, and a decrease in SOD activity ($p < 0.05$). Nuclear NF*k*B immunoreactivity also increased significantly in substantia nigra, jejunum, and colon from 7 days of ozone exposure to 90 days. ($p < 0.05$). In conclusion, the results indicate that exposure to ozone causes a chronic state of oxidative stress, decreasing the antioxidant capacity of total SOD and leading to a loss of regulation of inflammatory processes,

similar to what can occur in patients with Parkinson's disease. Funded by Grant IN-221521 to S.R.A PAPIIT-UNAM and CONAHCYT CVU 385286 for A.M.M.

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**Poster**

**PSTR018. Mechanisms of Neurotoxicity I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR018.15/M9

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH Grant MH085081
NIH Grant NS127364

**Title:** The knockdown of a putative amino acid transporter in the Malpighian tubules significantly increases sensitivity to lithium toxicity in Drosophila

**Authors:** J. KASUYA[1], Z. WYNOHRAD[2], ***T. KITAMOTO**[2];
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**Abstract:** Lithium is a simple alkali metal with chemical properties similar to those of sodium. However, it is highly effective in mitigating depressive or manic episodes in affective disorders and can diminish suicidal ideation. Recent studies also suggest that lithium may be useful in treating other psychiatric and neurological disorders, such as autism spectrum disorders and Alzheimer's disease. Despite its effectiveness, lithium does have its drawbacks. Firstly, the exact mechanisms underlying lithium's therapeutic effects remain largely unknown. Secondly, the therapeutic range of lithium is narrow, and it can have several side effects even at therapeutic concentrations.
To gain insights into the fundamental mechanisms underlying the efficacy and toxicity of lithium, we have been utilizing *Drosophila* genetics. Through our gene expression profiling analysis using adult flies, we identified *CG15088*, a putative amino acid transporter of the solute carrier 6 (SLC6) family, as one of the genes significantly upregulated in response to lithium treatment. Therefore, we named the transporter gene *Lithium-inducible SLC6 transporter* or *List*. Interestingly, loss-of-function mutations in *List* lead to a significant increase in sensitivity to lithium toxicity. The lithium sensitivity of *List* null mutants exhibits sexual dimorphism, with male mutants showing higher mortality than female mutants when fed lithium-containing food. *List* is primarily expressed in the nervous system, hind gut, and Malpighian tubules, which serve as the functional equivalent of the human kidney. Tissue-specific gene knockdown experiments using the *GAL4/UAS* binary expression system with *List-RNAi* indicate that reduced *List* expression in the Malpighian tubules is responsible for lithium-induced death in *List* mutants. Consistent with the assumed function of the LIST protein, the lithium sensitivity of *List* null mutants is mitigated by supplementing lithium-containing food with certain amino acids,

including glycine.
Overall, our studies have suggested that amino acids transported by the LIST protein in the kidney-like Malpighian tubules play a crucial role in resistance and sensitivity to lithium toxicity in *Drosophila*. It would be interesting to examine the extent to which these mechanisms are conserved in mammalian species, including humans.

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**Poster**

**PSTR018. Mechanisms of Neurotoxicity I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR018.16/M10

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** UFBA
FAPESB
CAPES

**Title:** Comparative cytotoxic analysis of three synthetic macamides present in Lepidium Meyenii

**Authors:** ***F. CARVALHO**[1,2], C. GOES[2], V. DA SILVA[2], Y. TIZABI[1], P. RIBEIRO[2];
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**Abstract:** *Lepidium meyenii* (Peruvian Maca), is an edible plant that has been used as a nutritional supplement worldwide due to its medicinal properties. Thus, macamides, the major bioactive compounds of Maca, are a unique class of non-polar, long chain fatty acid N-benzylamides with fertility-enhancing, neuroprotective, neuro-modulatory, anti-fatigue, anti-osteoporosis and potential anti-tumor effects. However, most of the studies have focused on the pharmacological activities of the extracts rather than their chemical composition. Recently, we showed that some extracts of *L. meyenii* roots may cause cytotoxicity in in-vitro culture of glioma cells. In contrast, macamide extracts exhibited potent anti-glioma activity in the same cultured cells. In this study we synthetized three macamides (M1, M2 and M3) and analyzed their cytotoxicity in pheochromocytoma PC12 cells. For that, confluent PC12 cell were treated with M1, M2 and M3 in concentration ranging from 0.1 - 500 µM for 48 h, and the cell viability was analyzed by MTT Test. We observed that concentrations higher than 250 µM of M1, 500 µM of M2, and higher than 250 µM of M3 were cytotoxic in PC12 cells. These results reinforce the bioactivity of macamides in neural tumor cells and provide the rationale for synthesizing synthetic derivatives of macamides to study their molecular mechanisms and potential neuroprotective and antitumor effects.

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**Poster**

**PSTR018. Mechanisms of Neurotoxicity I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR018.17/N1

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** The impact of space radiation on the circadian visual system in the retina and brain of female Wistar rats

**Authors: *D. D. SHUBONI-MULLIGAN**[1], A. BLACKWELL[1], R. BRITTEN[1], A. J. GALL[2]; [1]Eastern Virginia Med. Sch., Norfolk, VA; [2]Psychology, Hope Col., Holland, MI

**Abstract:** Radiation exposure has detrimental effects on tissue, causing DNA damage which can lead to necrosis. The eyes are a radiovulnerable organ, so exposure to radiation can cause cataract and damage to the retina that will lead to visual impairments. However, little is known about the impact of radiation on the circadian visual system. In space, astronauts are chronically exposed to whole body space radiation that can lead to the disruption of sleep and reduced performance in cognitive tasks, both factors that indicate possible issues at the level of the circadian visual system. Here we examined the eyes of animals exposed to galactic space radiation, at levels which will be experienced during a trip to Mars, to determine how the circadian visual system will be impacted by exposure. Adult female Wistar rats were exposed to radiation, 10 cGy of $^{4}$He ions (He) or Galactic Cosmic Ray Simulation - a mixture of ions and energy (GCRsim), and compared to sham controls. All animals received a unilateral injection of fluorescently labeled cholera toxin beta subunit into the left eye. After incubation, animals were PFA perfused and tissue collected including the lens, retinas, and brains. Damage to the lens of animals that received radiation was dramatically visible during extraction. Cloudy lens were observed in 66% of the GCRsim mice and 85% of He mice but only 25% of the sham animals. Additionally, both of the radiation groups contained many more malformations and disintegration of the structure. Previous work has indicated a reduction in general retina size after space radiation exposure. Therefore, we are quantifying melanopsin staining of ipRGC cells at the level of the retina, determining the level of tract tracer labeling within brain and histologically quantifying brain atrophy along the Retinohypothalamic Tract and in sleep/cognitive regions. Our previous work has demonstrated changes in brain structures based on temporal niche, aging and radiotherapy exposure; here, we will determine the impact of space radiation on the circadian visual system.


**Disclosures:** **D.D. shuboni-Mulligan:** None. **A. Blackwell:** None. **R. Britten:** None. **A.J. Gall:** None.

**Poster**

**PSTR018. Mechanisms of Neurotoxicity I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR018.18/N2

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NRF- 2020M2C8A2069337
NRF-2020R1C1C1006659

**Title:** The effects of low-dose-rate ionizing radiation on type II diabetes-induced cognitive impairment in db/db mice: Insights in to hippocampal gene profiling

**Authors:** Y. SON, Y. CHOI, S.-H. LEE, Y. JEONG, ***H.-J. LEE**;
Korea Inst. of Radiological & Med. Sci., Seoul, Korea, Republic of

**Abstract:** Diabetes is a chronic metabolic disorder that affects the body's ability to regulate blood glucose levels. Cognitive impairment is a prevalent complication of diabetes, significantly impacting affected individuals' quality of life. However, the effects of low-dose-rate radiation (LDIR) on the cognitive function and gene expression of db/db mice have not been extensively studied. Here, we used male diabetic (db/db) mice at 6 weeks of age as experimental animals and allowed them to acclimate for one week before starting the experiment. To investigate the effects of low-dose-rate radiation on the locomotor activity and cognitive function in db/db mice by conducting open field (OF) test and novel object recognition memory (NOR) tests. Additionally, we performed RNA sequencing (RNA-seq) analysis to study gene expression profiles in the hippocampus to elucidate the molecular mechanisms of LDIR-induced brain function changes. The OF test results showed a significant decrease in total distance, time spent in the center, and distance traveled in the center by db/db mice. However, no significant changes in locomotor activity were observed in db/db mice following LDIR exposure. In NOR test, LDIR exposure ameliorated the cognitive dysfunction observed in db/db mice. RNA-seq revealed 234 differentially expressed genes in the hippocampus of db/db mice compared with wild-type (WT) mice. Notably, immediate-early gene (IEG) expressions, associated with learning and memory

function in brain were significantly decreased in db/db mice compared to WT mice. However, exposure of low-dose-rate radiation resulted in a significant increase in IEGs expression compared with sham-exposed db/db mice. Therefore, our finding suggest that the ameliorative effect of low-dose-rate radiation on cognitive dysfunctions in db/db mice might be associated with changes in IEGs expression in the mouse brain.
**Acknowledgement**This work was supported by the National Research Foundation of Korea (NRF- 2020M2C8A2069337 and NRF-2020R1C1C1006659) funded by the Korean government Ministry of Science and ICT (MSIT).

**Disclosures:** **Y. Son:** None. **Y. Choi:** None. **S. Lee:** None. **Y. Jeong:** None. **H. Lee:** None.

**Poster**

**PSTR018. Mechanisms of Neurotoxicity I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR018.19/N3

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** KIRAMS grant 50535-2021
NRF grant 2020R1C1C1012154

**Title:** The Roles of Enteric Neuron in Intestinal Regeneration

**Authors: *H. JANG**, H.-J. LEE, S. SHIM, W. JANG, S. LEE;
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**Abstract:** Radiation-induced enteropathy is progressive disease of the intestines that occurs after abdominal or pelvic radiation therapy as well as the event of nuclear accidents or radiological terrorism. Exposure to a high dose of radiation cause severe damage of gastrointestinal (GI) regeneration with depletion of the pool of intestinal stem cells. Enteric neuron was first reported for its major role in intestinal motility, but is now known to be responsible for many aspects of intestinal physiologic functions to maintain intestinal homeostasis. to stress challenge. Here, we explored the roles of enteric neuron for the management of radiation-induced impaired regeneration. We identified that radiation-induced enteropathy were characterized by a reduced number of enteric neurons defining neuropathy and delayed GI motility. Treatment of prucalopride, a well-known 5-HT4 agonist and prokinetics, resulted in prevention of delayed intestinal motility and significantly increased the number of peripherin, HuC/D, and nNOS-positive enteric neurons with recovered histological damage in irradiated (IR) mouse. We also determined that enteric neuron of longitudinal muscle/myenteric plexus reinforced epithelial regeneration and mitigated acute radiation-induced enteropathy in intestinal organoids and mouse model. Especially, neuropeptide Y (NPY), a neurotransmitter secreted by enteric neuron, accelerated regenerative ability of intestinal organoids on radiation damage. Finally, we found that NPY application alleviated acute radiation-induced enteropathy mouse model. Taken together, these results indicated that enteric neuron reinforced epithelial regeneration in

radiation-damaged epithelial cells and that protection of ENS is a novel therapeutic target that can be used to alleviate radiation-induced GI damage.

**Disclosures:** **H. Jang:** None. **H. Lee:** None. **S. Shim:** None. **W. Jang:** None. **S. Lee:** None.

**Poster**

**PSTR019. Neuroprotective Mechanisms: Pharmacological Approaches**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR019.01/N4

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** A high-throughput screening strategy to identify inhibitors of the Sterile Alpha and TIR Motif Containing 1 (SARM1) enzyme

**Authors:** *A. S. A. MADY, **D. J. BLACKWELL**, N. R. PERL, T. J. WIGLE, B. W. DORSEY, W. D. CHURCH, D. PATEL, D. C. MOEBIUS, A. H. ABUARQOUB, A. G. SANTOSPAGO, C. R. MAJER, H. KEILHACK, K. W. KUNTZ;
Ribon Therapeutics, Inc., Cambridge, MA

**Abstract:** Sterile Alpha and TIR Motif Containing 1 (SARM1) is a key protein involved in the degeneration of axons. Through dimerization of its toll-interleukin receptor (TIR) domain, SARM1 hydrolyzes nicotinamide adenine dinucleotide ($NAD^+$) to nicotinamide and cyclic adenosine diphosphate ribose (cADPR). SARM1's NADase activity plays a crucial role in the process of axon degeneration. Upon axonal injury or damage, SARM1 is activated leading to the depletion of $NAD^+$. This results in the disruption of energy production and fragmentation of the axon, contributing to axonal degeneration. Hence, inhibiting SARM1 function is an attractive neuroprotective strategy in neurodegenerative diseases. In this study, a luminescence-based enzymatic assay was developed in which the SARM1 TIR domain was activated by immobilization leading to the hydrolysis of $NAD^+$. Utilizing this assay, we screened a diverse small-molecule library of 155,000 compounds. The screening campaign identified multiple hit compounds that demonstrated SARM1 inhibition. These hits were validated using counter assays followed by dose-response studies. Several compounds were confirmed to selectively inhibit full-length SARM1. Using surface plasmon resonance and thermal shift assays we demonstrated the inhibitors exhibited an $NAD^+$-dependent uncompetitive mechanism of inhibition. Furthermore, structure-activity relationship (SAR) analysis to elucidate the chemical features responsible for modulating SARM1 activity led to the development of a series of potent inhibitors. X-ray co-crystal structures revealed the formation of an inhibitor-ADPr adduct, thereby confirming the $NAD^+$-dependent mechanism of action. This structural information enabled the identification of key structural motifs and functional groups critical for activity, offering valuable insights for further optimization. Ultimately, a low nanomolar SARM1 inhibitor was optimized exhibiting cellularSARM1 inhibition and favorable pharmacokinetic properties. The compound was evaluated in a mouse sciatic nerve axotomy model and showed in vivo target engagement based on neurofilament light chain (NfL) modulation. Overall, our high-

throughput screening strategy led to the identification of small molecule modulators of SARM1 activity that were characterized using a comprehensive set of biochemical, biophysical, and cellular assays. These modulators hold promise as tools to further study the role of SARM1in various neurodegenerative disease models.

**Disclosures:** **A.S.A. Mady:** A. Employment/Salary (full or part-time); Ribon Therapeutics, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options. **D.J. Blackwell:** A. Employment/Salary (full or part-time); Ribon Therapeutics, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options. **N.R. Perl:** A. Employment/Salary (full or part-time); Ribon Therapeutics, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options. **T.J. Wigle:** A. Employment/Salary (full or part-time); Ribon Therapeutics, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options. **B.W. Dorsey:** A. Employment/Salary (full or part-time); Ribon Therapeutics, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options. **W.D. Church:** A. Employment/Salary (full or part-time); Ribon Therapeutics, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options. **D. Patel:** A. Employment/Salary (full or part-time); Ribon Therapeutics, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options. **D.C. Moebius:** A. Employment/Salary (full or part-time); Ribon Therapeutics, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options. **A.H. Abuarqoub:** A. Employment/Salary (full or part-time); Ribon Therapeutics, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options. **A.G. Santospago:** A. Employment/Salary (full or part-time); Ribon Therapeutics, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options. **C.R. Majer:** A. Employment/Salary (full or part-time); Ribon Therapeutics, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options. **H. Keilhack:** A. Employment/Salary (full or part-time); Ribon Therapeutics, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options. **K.W. Kuntz:** A. Employment/Salary (full or part-time); Ribon Therapeutics, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock options.

**Poster**

**PSTR019. Neuroprotective Mechanisms: Pharmacological Approaches**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR019.02/N5

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH Interagency Agreement (AOD22011-001-00000 & AOD23004-001-00000; MOA-AI-21002-01)
Oak Ridge Institute of Science and Education appointments (DE-SC0014664)

**Title:** Anticonvulsant efficacy of midazolam in the planarian Dugesia dorotocephala

**Authors: *M. CONROY**, N. HALL, H. MCCARREN;
Neurosci., USAMRICD, Aberdeen Proving Ground, MD

**Abstract:** *Dugesia dorotocephala* is an abundant species of aquatic planaria that has emerged as an attractive model organism for screening of neurotoxic compounds and potential antidotes. Planaria possess homologs to most of the major neurotransmitter systems found in mammals, and they have demonstrated specific behaviors in response to pharmacological stimuli that parallel those of mammals. In particular, planaria exhibit seizure-like activity such as writhing, c-shaped hyperkinesias, and corkscrewing when they're exposed to known convulsant compounds. The goal of this study was to verify that planaria can serve as a non-mammalian screening tool for neurotoxic compounds and associated antidotes. In this study, planarians were exposed to one of five convulsant compounds: soman, picrotoxin, strychnine, methyl hydrazine, 4-aminopyridine, and nicotine. After preliminary dose-ranging studies for each convulsant, chemicals were co-applied with the benzodiazepine midazolam to determine if this first-line anticonvulsant could prevent neurotoxic effects in the planaria model system. During each 1-hour exposure, Ethovision 17.0 software was used to track distance traveled and activity of individual planarians in a 24-well plate. Worms exposed to 4-aminopyridine, soman, methyl hydrazine, and strychnine all had significant dose-dependent reductions in activity over the first 10 minutes of exposure, with 180µM midazolam fully attenuating motor symptoms. Alternately, midazolam enhanced seizure-like activity of nicotine and prevented the prolonged tetanic state induced by nicotine alone. Notably, doses of midazolam above 100µM were generally required for therapeutic efficacy, but when administered in the absence of other chemicals they induced seizure-like activity in the planaria model. Overall, our results indicate that *Dugesia dorotocephala* consistently demonstrate seizure-like activity in response to known convulsants with differing mechanisms of action and respond to treatment with the benzodiazepine midazolam, making them promising as a high-throughput screening model for seizurogenic compounds and anticonvulsant countermeasures.

**Disclosures: M. Conroy:** None. **N. Hall:** None. **H. McCarren:** None.

**Poster**

**PSTR019. Neuroprotective Mechanisms: Pharmacological Approaches**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR019.03/N6

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** FAPESP # 2018/05006-0
FAPESP # 2022/13353-8

**Title:** Acute sciatic nerve repair with 4-hydroxi-tempo (Tempol) and polyetilenglycol axon fusion protocol

**Authors: A. SALAMANCA**[1], L. P. CARTAROZZI[1], L. MELO-THOMAS[2], A. S. VIEIRA[3], *A. OLIVEIRA[1];
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**Abstract:** Peripheral nerve transection is a common clinical problem that requires acute surgical repair usually carried out by end-to-end neurorrhaphy. However, neuropathic pain, paralysis, and muscle weakness may persist for several months or even become permanent. After axonotmesis, Wallerian degeneration (WD) takes place in the distal stump, and axonal regeneration is slow resulting in limited sensorimotor recovery, causing muscle atrophy. A groundbreaking approach is the axon fusion acutely after injury, using polyethylene glycol (PEG) as a fusogen, avoiding WD, and resulting in prompt electrophysiological recovery. The present study aimed to evaluate the effectiveness of 4-hydroxy-tempo (Tempol) in combination with PEG fusion following sciatic nerve transection. Thus, adult female Lewis rats were subjected to a sciatic nerve transection followed by either end-to-end neurorrhaphy (NRR, N=6) or Tempol-PEG-fusion (T-Fusion, N=3). Electroneuromyography was used to record the compound action potential (CAP) evoked proximal to the surgical repair. Latency, amplitude, and duration of the CAPs were compared between groups, and sensorimotor function was evaluated with the walking track test (CatWalk system) up to the eighth-week post-injury and repair. The rats were then euthanized and the nerves were evaluated with Sudan black staining and immunohistochemistry against neurofilaments. The experiments were approved by the Institutional Committee for Ethics in Animal Use (CEUA/IB/UNICAMP, Brazil, protocol number 5875-1/2021). Electrophysiology demonstrated that T-Fusion rescued close-to-normal latency ($p=0.0007$), duration ($p<0.0001$), and amplitude ($p=0.0006$) immediately after repair, in contrast to NRR, which showed complete loss of function. T-fusion also showed significant improvement in the peroneal functional index ($p=0.0275$), and max contact ($p=0.0032$) throughout the evaluation period, which was aligned with the nerve environment preservation seen with the Sudan black and neurofilament immunolabeling analyses. Overall, the results suggest that the T-Fusion protocol produces greater motor improvement compared to end-to-end neurorrhaphy, the gold standard surgical treatment for peripheral nerve transection.

**Disclosures: A. Salamanca:** None. **L.P. Cartarozzi:** None. **L. Melo-Thomas:** None. **A.S. Vieira:** None. **A. Oliveira:** None.

**Poster**

**PSTR019. Neuroprotective Mechanisms: Pharmacological Approaches**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR019.04/N7

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** ICGEB Arturo Falaschi postdoctoral fellowship

**Title:** Comparative Effects of Stevia and Aspartame on Behavioral Markers, Brain Glucose Homeostasis and Redox Status in Lobster Cockroach; Nauphoeta cinerea (Blattodea: Blaberidae) Model

**Authors: *O. B. OGUNSUYI**[1], D. O. OLATUNDE[2], O. C. OLAGOKE[4], G. OBOH[3], J. B. T. DA ROCHA[5];
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**Abstract:** Brain glucose homeostasis is critical to the physiological condition of humans and its dysregulation is critical to the pathophysiology of several diseases including diabetes mellitus and Alzheimer´s disease. Alternative/non-caloric sweeteners, have become the mainstay of food industries to strategically reduce the prevalence of glucose-related disorders including diabetes mellitus and its co-morbidities. However, their acceptance has been greeted with mixed reactions regarding their effect on glucose homeostasis. This study investigated the effect of aspartame and stevia on behavioral indices, glucose homeostasis and redox status in head of streptozotocin (STZ)-induced lobster cockroach (*Nauphoeta cinerea* [Blattodea: Blaberidae]) model of brain glucose metabolic dysregulation. The cockroach nymphs (male and female) were divided into 6 groups (of 40 cockroaches per group) of control (group 1), 4% dietary inclusion of aspartame alone (group 2) 4% dietary inclusion of stevia alone (group 3), STZ-induced (20 µL of 74 mmol dorsal-thoracic injection of STZ/nymph; group 4), STZ-induced+ dietary inclusions of 4% aspartame (group 5) and STZ-induced+ dietary inclusions of 4% aspartame (group 6) for seven days. Thereafter, the cockroaches were observed for survival rate, behavioral markers followed by head homogenization and assay for glucose, trehalose and triglyceride contents, as well as redox markers. The results showed that STZ significantly impaired the behavioral patterns of the cockroaches including total distance traveled, maximal speed and turn angle among others. However, a significant amelioration was observed in STZ-induced cockroaches administered stevia when compared to aspartame. Furthermore, there was significant amelioration in the elevated brain glucose, reactive oxygen species, lipid peroxidation, catalase and glutathione-S-transferase activity, as well as reduced trehalose and triglyceride levels in STZ-induced cockroaches administered stevia compared to aspartame. These results therefore suggests that stevia rather than aspartame significantly mitigates behavioral and biochemical indices of brain glucose metabolic dysregulation in lobster cockroaches and might be considered choice sweetener under glucose metabolic dysregulation.

**Disclosures: O.B. Ogunsuyi:** None. **D.O. Olatunde:** None. **O.C. Olagoke:** None. **G. Oboh:** None. **J.B.T. da Rocha:** None.

**Poster**

**PSTR019. Neuroprotective Mechanisms: Pharmacological Approaches**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR019.05/N8

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** PAPIIT, UNAM, IN228420.

**Title:** Prolactin-induced neuroprotection against glutamate excitotoxicity is mediated by via PI3K/AKT and NF-κB signaling pathways in primary cell culture of hippocampal neurons

**Authors: *G. MOLINA SALINAS**[1], V. RODRÍGUEZ-CHÁVEZ[2], B. MARTÍNEZ-NÁJERA[2], A. MARTÍNEZ-IBARRA[2], M. CERBON[3];
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**Abstract:** Prolactin (PRL) is a peptide pleiotropic hormone. In the brain is associated with several functions including maternal behavior, neurogenesis, among others. Recently, it has been reported that PRL has an important role in neuroprotection against excitotoxicity damage, produced by both, glutamate (Glu) and kainic acid (KA), *in vitro* and *in vivo* models. However, the molecular mechanisms involved in PRL's neuroprotective effects in the hippocampus have not been completely understood. The aim of the present study was to assess the signaling pathway by which PRL promotes neuroprotection in primary cultures of rat hippocampal neurons that were administrated with Glu excitotoxicity (Glu, 50 μM/1h). Hippocampal neurons were exposed to different treatments: 20 ng/ml of PRL, PRL+Glu (20 ng/ml/ 50μM), inhibitor LY294002 (50 μM/ml) and the combination LY294002+PRL+Glu (50 μM, 20 ng/ml/ 50μM). Here we show, that phosphoinositide 3-kinases/Protein Kinase B (PI3K/AKT) signaling pathway activation was observed after PRL treatment promoting neuronal survival. In addition, subsequent AKT activation and its target protein NF-κB, promoted the up-regulation of the survival gen *Bcl-2* and antioxidant gen *Nrf2* expression. Conversely, after Glu administration and the inhibition were abolished. Our result suggests that PI3K/AKT and NF-κB signaling pathways are involved to PRL-induced neuroprotection, promoting survival genes expression. Decoding signaling pathways induced by PRL during neuroprotection in the hippocampus is relevant in the design for futures therapies to reduce the damage in neurodegenerative diseases. This study received funding from PAPIIT, UNAM, IN228420.

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**Poster**

**PSTR019. Neuroprotective Mechanisms: Pharmacological Approaches**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR019.06/O1

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** CONACYT scholarship grant 663120

**Title:** Hormetic effect of erythropoietin confers cytoprotection in SH-SY5Y cells subjected to oxygen and glucose deprivation and reoxygenation damage

**Authors: *A. MARIN LOPEZ**, M. RIVERA CERVANTES;
Univ. de Guadalajara, Guadalajara, Mexico

**Abstract:** Erythropoietin is a glycoprotein with neuroprotective properties against ischemic damage; however, the high doses usually used to exert neuroprotection are associated with undesirable side effects. Hormesis is characterized by a biphasic dose-response in which low or intermediate doses of a molecule provide greater benefits; however, the underlying mechanisms of the hormetic effect of erythropoietin remain poorly understood. In this sense, the aim of this work was to evaluate the hormetic effect of recombinant human erythropoietin (rhEPO) on cytoprotection and gene expression of erythropoietin, erythropoietin receptor, beta common receptor, and anti-apoptotic gene Bcl-xL in a model of oxygen and glucose deprivation (OGD) and reoxygenation damage. SH-SY5Y cells were subjected to 5, 15, and 24 h of OGD (98% $N_2$ and 2% O2) and 20, 24, and 24 h of reoxygenation, respectively. To determine the hormetic-like effect of erythropoietin on cytoprotection the cells were treated with different concentrations of rhEPO (100, 75, 50, 25, and 12.5 U/mL) during the 24 h reoxygenation period and after 15 h of OGD.SH-SY5Y cells were subjected to 5, 15, and 24 h of OGD (98% $N_2$, 2% $O_2$) and 20, 24, and 24 h of reoxygenation, respectively. To determine the hormetic-like effect of erythropoietin on the cytoprotection the cells were treated with different concentrations of rhEPO (100, 75, 50, 25, and 12.5 U/mL) during the 24 h reoxygenation period and after 15 h of OGD. Cell viability was evaluated using the MTT assay, and the relative gene expression was measured using real-time PCR and the $2^{-\Delta\Delta Ct}$ method. Our findings revealed a hormetic-like cytoprotective response, in which only the dose of 50 U/mL resulted in a statistically significant decrease in cell viability loss compared to the OGD group ($p<0.05$). We did not observe changes in the mRNA expression of the receptors or anti-apoptotic genes after a 4 h erythropoietin treatment neither in the optimal dose (50 U/mL) or the high dose (100 U/mL), likely due to the short exposure duration. Nevertheless, an increase in erythropoietin mRNA expression was observed following oxygen and glucose deprivation and reoxygenation damage. These results demonstrate the hormetic-like cytoprotective response of erythropoietin against this type of injury; however further investigations with longer erythropoietin treatments are necessary to assess changes in the gene expression of receptors and anti-apoptotic molecules.

**Disclosures: A. Marin Lopez:** None. **M. Rivera Cervantes:** None.

**Poster**

**PSTR019. Neuroprotective Mechanisms: Pharmacological Approaches**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR019.07/O2

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Lack of neuroprotection by delta-8 THC against an in vitro oxidative stress injury.

**Authors: *A. REED**, M. H. GRIDER;
Neurosci., High Point Univ., High Point, NC

**Abstract:** Oxidation of cellular proteins and lipids is a shared signaling mechanism across diverse neuronal injuries and diseases. As cannabinoids can display anti-oxidant properties, we tested whether delta-8 THC would provide neuroprotection against an oxidative injury. An optimal concentration of hydrogen peroxide ($H_2O_2$) was determined empirically with a dose-dependent curve, and the concentration that killed approximately 30% of the cells was selected for other experiments. Differentiated SH-SY5Y cells were then incubated with delta-8 THC before, or concurrently, with $H_2O_2$. Cell viability was determined using a chromogenic MTT reaction detected with a spectrophotometric plate reader. We find that delta-8 THC, alone, did not result in a change in cell viability. Additionally, delta-8 was not effective at attenuating the loss of cell viability associated with the $H_2O_2$ injury. We are continuing our investigation of cannabinoid neuroprotection in different cell lines and with different injury models.

**Disclosures: A. Reed:** None. **M.H. Grider:** None.

**Poster**

**PSTR019. Neuroprotective Mechanisms: Pharmacological Approaches**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR019.08/O3

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** Sage Therapeutics

**Title:** Neurosteroid allopregnanolone elevates IL-10 production through the endosomal TRIF-dependent TLR4 signaling pathway

**Authors: I. BALAN**, A. GRUSCA, T. K. O'BUCKLEY, G. BOERO, *A. L. MORROW;
Psychiatry and Pharmacol., UNC Sch. of Med., Chapel Hill, NC

**Abstract:** We recently found that the neurosteroid allopregnanolone (3α,5α-THP) decreases proinflammatory cytokine and chemokine levels through inhibition of the MyD88-dependent toll-like receptor (TLR) signaling pathways in macrophages and brain. The MyD88-dependent TLR4 pathway is mediated by the adaptors MyD88 and TIRAP and operates at the plasma

membrane. TLR4 also signals through a TRIF-dependent pathway that is initiated by the adaptors TRIF and TLR4-specific TRAM in endosomes. Additionally, activation of the p110δ isoform of PI(3)K is known to induce anti-inflammatory IL-10 after the TLR4 transition from the plasma membrane to endosomes, while inducing TIRAP degradation and thus dampening TIRAP-MYD88-mediated proinflammatory signaling (Aksoy et al. 2012). We examined the effects of 3α,5α-THP on the levels of IL-10 as well as on activation of both TRIF-dependent endosomal TLR4 and PI(3)K-p110δ in the male and female amygdala of alcohol-preferring P rats that demonstrated innately activated TLR4. The administration of 3α,5α-THP (10 mg/kg, IP) elevated IL-10 (+13.2±6.5%, p=0.04) and BDNF (+21.1±11.5%, p=0.04) levels in males, but not females. Accordingly, in males, there was also elevation of phosphorylated/activated pTRAM (+86.4±28.4%, p=0.0007) indicating activation of the endosomal TRIF-dependent TLR4 signals, whereas in females, pTRAM (-16.2±7.2%, p=0.04) was inhibited by 3α,5α-THP. In males, the TRAM-dependent TLR4 activation is accompanied by elevation of the transcription factor SP1 (+122.2±74.9%, p=0.03) and PI(3)K-p110δ (+61.6±21.6%, p=0.009), as well as a reduction of TIRAP (-13.7±6.0%, p=0.02). In contrast, other evaluated potential signaling pathway members pCREB, HSP70 and c-Maf demonstrated no response to 3α,5α-THP, while the level of pAkt (-34.2±26.4%, p=0.04) was inhibited by 3α,5α-THP. Moreover, 3α,5α-THP facilitated TLR4 (+26.2±15.7%, p=0.048) but not TLR3 accumulation in endosomes and facilitated the transition between early (EEA1 levels: no difference, p=0.60) and late (Rab7 levels: +60.5±29.5%, p=0.04) endosomes. To further determine whether the TRIF-dependent TLR4 signaling pathway is involved in the IL-10 production, RAW264.7 cells that innately expressed TLR4 were transfected with TRIF siRNA (20nM, 72h). The downregulation of TRIF (-88.3±43.3%, p=0.04) led to the reduction in IL-10 (-41.6±14.2%, p=0.01). Overall, this work demonstrates that 3α,5α-THP can enhance endosomal TLR4-TRIF anti-inflammatory signals and elevate anti-inflammatory IL-10 while inhibiting MyD88-dependent TLR pro-inflammatory signals and pro-inflammatory mediators.

**Disclosures:** **I. Balan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Provisional patent on anti-inflammatory effects of allopregnanolone and related neurosteroids. **A. Grusca:** None. **T.K. O'Buckley:** None. **G. Boero:** None. **A.L. Morrow:** 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.; Sage Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Provisional patent on anti-inflammatory effects of allopregnanolone and related neurosteroids.

**Poster**

**PSTR019. Neuroprotective Mechanisms: Pharmacological Approaches**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR019.09/O4

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** Research Grants Council HK General Research Fund (14107118)
Research Grants Council HK General Research Fund (14122019)

**Title:** A peptide inhibitor that rescues polyglutamine-induced synaptic defects and cell death through suppressing RNA and protein toxicities

**Authors: *E. CHAN**[1], L. LEONG[2], I. PENG[2], S. CHEN[2];
[1]Sch. of Life Sci., [2]The Chinese Univ. of Hong Kong, Hong Kong, Hong Kong

**Abstract:** Polyglutamine (polyQ) diseases, including spinocerebellar ataxias and Huntington's disease, are progressive neurodegenerative disorders caused by CAG triplet-repeat expansion in the coding regions of disease-associated genes. In this study, we found that neurotoxic small CAG (sCAG) RNA species, microscopic CAG RNA foci, and protein aggregates exist as independent entities in cells. Synaptic defects and neurite outgrowth abnormalities were observed in mutant polyQ-expressing mouse primary cortical neurons. We examined the suppression effects of the CAG RNA-binding peptide beta-structured inhibitor for neurodegenerative diseases (BIND) in mutant polyQ-expressing mouse primary cortical neurons and found that both impaired synaptic phenotypes and neurite outgrowth defects were rescued. We further demonstrated that BIND rescued cell death through inhibiting sCAG RNA production, mutant CAG RNA foci formation, and mutant polyQ protein translation. Interestingly, when the expanded CAG repeats in the mutant CAG transcript was interrupted with the alternative glutamine codon CAA, BIND's inhibitory effect on mutant protein aggregation was lost. We previously demonstrated that BIND interacts physically and directly with expanded CAG RNA sequences. Our data provide evidence that the BIND peptide associates with transcribed mutant CAG RNA to inhibit the formation of toxic species, including sCAG RNA, RNA foci, and polyQ protein translation and aggregation. We further developed a BIND peptide variant which displays improved bioactivities against polyQ toxicities.

**Disclosures:** **E. Chan:** None. **L. Leong:** None. **I. Peng:** None. **S. Chen:** None.

**Poster**

**PSTR019. Neuroprotective Mechanisms: Pharmacological Approaches**

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**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR019.10/O5

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Small molecule n-ter-butyl-hydroxylamine reduces neuroinflammation, motor dysfunction & epilepsy in a mouse model of cln1 disease.

**Authors: *Z. FYKE**[1], S. SAGOSHI[2], K. KOSTER[4], S. ALFORD[2], A. YOSHII[3];
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**Abstract:** Infantile neuronal ceroid lipofuscinosis (CLN1) is a devastating lysosomal storage disease, whose symptoms include blindness, seizures, and psychomotor dysfunction leading to premature death by 5 years of age. CLN1 is caused by mutation of palmitoyl-protein thioesterase *(PPT1)*, a depalmitoylating enzyme. Loss of function of this critical depalmitoylation enzyme results in the aggregation of overly palmitoylated proteins in the lysosome, generating a cardinal histological feature of CLN1 known as autofluorescent storage material (AFSM). These intraneuronal accumulations coincide with microglial activation and reactive gliosis. Importantly, disruption of proteostasis, microglial activation and reactive gliosis are also present in common, multifactorial neurological diseases including Alzheimer's Disease. Therefore, investigations into the pathological mechanisms of CLN1 will have broad implications for therapeutic development across diseases. Here, we studied the effect of supplementation with a PPT1 mimetic small molecule that cleaves palmitate from palmitoylated proteins, N-tert-butyl hydroxylamine (NtBuHA), in the *Ppt1*$^{-/-}$ mouse model of CLN1. Treatment of *Ppt1*$^{-/-}$ mouse primary neuron cultures with NtBuHA resulted in a dose-dependent reduction of AFSM accumulation. Similarly, chronic oral administration of NtBuHA to *Ppt1*$^{-/-}$ mice significantly diminished AFSM aggregation at 2 crucial disease-relevant time points. Furthermore, NtBuHA significantly ameliorated GFAP expression, a marker of neuroinflammation, and partially reversed pro-inflammatory microglial morphology compared to untreated *Ppt1*$^{-/-}$ animals. Additionally, we tested the effect of NtBuHA treatment on locomotor function, as ataxia is characteristic of PPT1 deficiency. Our data indicate that treatment with NtBuHA rescues motor coordination. Finally, unilateral motor and visual cortical EEG recordings in freely-behaving *Ppt1*$^{-/-}$ mice treated with NtBuHA,demonstrated that drug treatment completely attenuated epileptic activity at the disease endpoint. These findings point to NtBuHA as the potential first clinical treatment for CLN1 disease, suggesting therapeutic replacement could potentially attenuate the deficits of *PPT1* $^{-/-}$ alongside varieties of other neurodegenerative diseases.

**Disclosures:** **Z. Fyke:** 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.; Circumvent Pharmaceuticals. **S. Sagoshi:** None. **K. Koster:** None. **S. Alford:** None. **A. Yoshii:** 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.; Circumvent Pharmaceudicals.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.01/Web Only

**Topic:** C.09.Stroke

**Title:** Large Language Model Generated Prompting as Speech Therapy Adjuvant for a Patient with Expressive Aphasia

**Authors: *E. ALTSCHULER**[1], M. THORNTON[2], J. SAYEGH[1], N. THORNTON[1], J. IOZZIA[1], R. PAK[1], A. LEKSHMINARAYANAN[3], E. VILLAMOR[1];
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**Abstract:** Increasing speech production in patients with expressive aphasia as a consequence of stroke or other brain lesions remains a challenge; novel approaches are needed. Literature from decades ago as well as our clinical experience demonstrate that expressive aphasia patients can readily produce antonyms, but have significant difficulty with producing synonyms. A recent case report suggested further exploration of sentence completion as a tool to use in treatment of patients with expressive aphasia. Recently released large language models (LLMs) are very useful for generating sentences or phrases to be completed and antonyms or other related type prompts. For a patient with post-stroke expressive aphasia, we found that with LLM-generated prompts the patient was able to produce half of target words not said after an initial sentence description clue. We found that when the target word was at the end of the sentence or phrase to be completed this was a more powerful queue/prompt than if the target word was elsewhere (e.g., Call 911 in case of emergency. vs. The canary in the coal mine. Other powerful cues were antonyms (e.g., “Not a smile but a frown”), opposites (“Ladies and gentlemen”), and what we call “pseudo-opposites,” e.g., “Not a lime but a lemon." Conversely, surprisingly, rhymes were not useful as prompts, e.g., “Word beginning with ‘c’ rhyming with antelope,” did not evoke “cantaloupe” as a response. A LLM based approach, for example utilizing a phone app, has a number of advantages over traditional speech therapy: (1) the app can be with the patient at all times. The app makes moot issues of time, money, logistics to generate sentence completion and other prompting cues, (2) in particular, scene-aware apps should be developed. For example, taking a picture of a restaurant menu and prompting the patient based on this, (3) Crucially, LLMs work in any language which is particularly useful if the speech therapist does not speak the patient’s preferred language, (4) LLMs can learn to individualize prompts. The potential utility of LLM prompting for patients with aphasia is consistent with feedforward models of speech production. Further study and development LLMs to generate sentence completion, antonyms, opposites and other prompts to generate useful speech in patients with expressive aphasia are warranted. Privacy concerns also need to be studied.

**Disclosures: E. Altschuler:** None. **M. Thornton:** None. **J. Sayegh:** None. **N. Thornton:** None. **J. Iozzia:** None. **R. Pak:** None. **A. Lekshminarayanan:** None. **E. Villamor:** None.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.02/O6

**Topic:** C.09.Stroke

**Support:** NIH Grant RF1AG058603

**Title:** Photobiomodulation treatment inhibits stroke-induced cerebrovascular senescence and enhances angiogenesis

**Authors: *X. ZONG**, Y. FENG, Z. HUANG, X. MA, Q. ZHANG;
Louisiana State Univ. Hlth. Sci. Ctr. Neurol. Dept., Shreveport, LA

**Abstract: Photobiomodulation Treatment Inhibits Stroke-induced Cerebrovascular Senescence and Enhances Angiogenesis**
**Department of Neurology, Louisiana State University Health Sciences Center, Shreveport, LA, 1501 Kings Highway, LA 71103 USA.**
**Abstract** Recent work indicates that photobiomodulation (PBM) can beneficially alter the pathological status of several cerebrovascular diseases. However, the underlying mechanism remains unclear. This study aimed to investigate the effects of PBM on vascular senescence and angiogenesis in rats using the photothrombosis (PT) stroke model. Additionally, we sought to explore the effect of PBM treatment on oxygen-glucose deprivation (OGD)-induced cellular senescence and angiogenesis related signal *in vitro*. We demonstrated that 2-minute daily PBM (CW, 808 nm, 350 mW/cm2 at scalp level) for 7 days significantly reduced cerebrovascular permeability, as confirmed by FITC staining. Furthermore, PBM treatment inhibited the expression of senescence associated markers **(**senescence green and p21), while increased the vessel associated Ki67 level in the peri-infarct region after ischemic stroke. To further validate the effects of PBM on cerebrovascular cells, we conducted experiments using brain endothelial cells. Our study revealed that single-dose PBM treatment could decrease the senescence associated marker (p16 and p21) in brain endothelial bEND.3 cells. Simultaneously, PBM treatment increased the levels of Ki67 and vascular endothelial growth factor (VEGF), while decreasing the endostain level following OGD exposure. In summary, our results indicate that PBM treatment is effective in reducing vascular permeability, mitigating the vascular senescence, as well as promoting angiogenesis. The potential mechanisms are associated with up regulated VEGF and down regulated endostain levels following ischemia and PBM therapy.
**Keywords:** angiogenesis, cerebrovascular senescence, photobiomodulation, stroke

**Disclosures: X. zong:** None. **Y. Feng:** None. **Z. Huang:** None. **X. Ma:** None. **Q. Zhang:** None.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.03/O7

**Topic:** C.09.Stroke

**Title:** Structural brain correlates of brain-computer interface performance after stroke

**Authors:** K. GRIGORYAN[1], D. MASRI[2], M. WAGNER[3], B. KALLOCH[4], C. J. STEELE[5], A. ANWANDER[1], A. VILLRINGER[2], ***B. SEHM**[1];
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**Abstract:** BCI interventions have the potential to enhance motor deficits even in the chronic phase after stroke. The effectiveness of such interventions, however, varies considerably among individual patients. This in turn might be related to interindividual differences in the ability to learn to control the BCI. In this study, we aimed to investigate whether residual structural connectivity as assessed by diffusion-weighted imaging (DWI) might serve as a predictor of BCI performance. We performed a clinical study in 21 chronic stroke patients (5 females, age: 60.8 ± 8.7, time since stroke in months: 53.8 ± 44.5), randomized into experimental (n = 11) and control groups (n = 10) in a longitudinal crossover design with delayed start. Both groups underwent 6 days of BCI training and were assessed pre- and post-training using the Fugl-Meyer Upper Extremity (FM-UE) clinical scale of motor impairment. The BCI training consisted of wrist dorsiflexion motor imagery while receiving visual and tactile feedback. Baseline, pre-training, post-training, and follow-up functional and structural MRI scans were conducted for all participants. Here, we used voxel-wise fractional anisotropy (FA, computed from the diffusion tensor) at baseline for correlation with the accuracy in BCI performance. Our results show that patients learned to control the BCI but exhibited high inter-individual variability. On average, the greatest improvement in accuracy was present on the second day of training, and followed by stable performance across the following days. We found that FA was positively correlated with improved accuracy in non-lesioned brain regions including the superior longitudinal fascicle, corona radiata, corticospinal tract, and inferior fronto-occipital fascicle. Our findings demonstrate a connection between residual white matter microstructure supporting brain connectivity and BCI performance after stroke.

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**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.04/O8

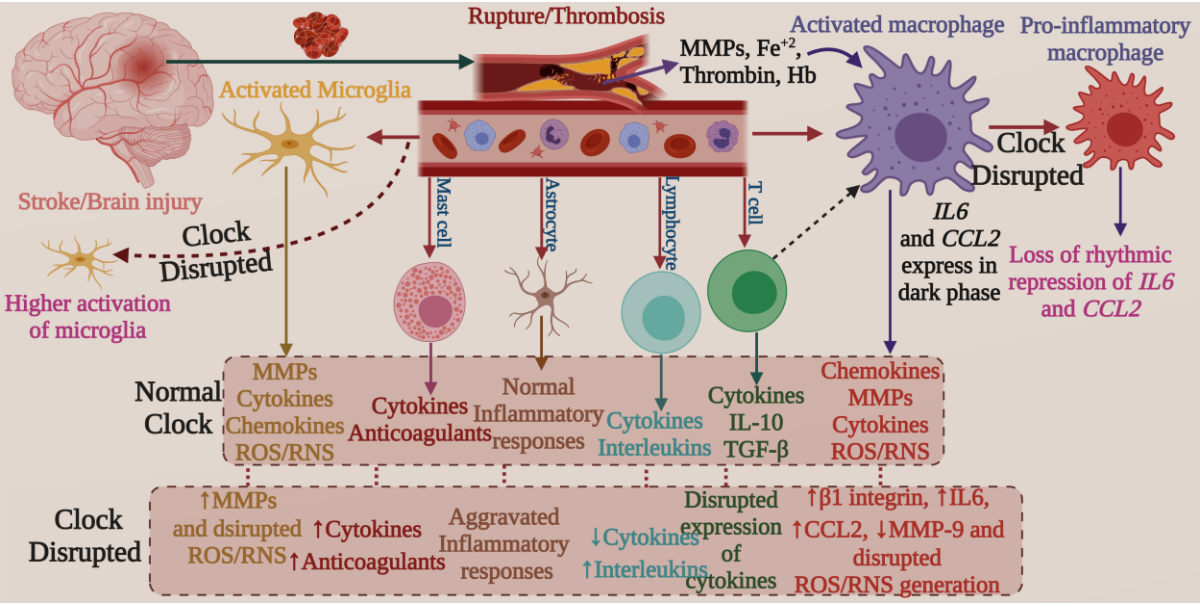
**Topic:** C.09.Stroke

**Support:** Chinese Postdoctoral Science foundation Grant 2020M67229
Henan Research grant for young scientists No.
The national foreign expert program QN2022026001L

**Title:** Investigating molecular links between intracerebral hemorrhage and circadian system

**Authors: *S. KHAN**[1,2], R. SIDDIQUE[3];
[1]The Univ. of Haripur, Haripur, Pakistan; [2]The Second Affiliated Hosp. of Zhengzhou Univ., Zhengzhou, China; [3]Zhengzhou Univ., Zhengzhou, China

**Abstract:** Altered circadian rhythms may increase the risk of stroke by disrupting the associated immunological processes. The circadian clock modulates the regulation of immune cells and neurotransmitters, indicating that circadian rhythms can influence the progression and recovery of stroke or intracerebral hemorrhage (ICH). Investigations are needed to determine how circadian rhythms are linked with ICH progression and recovery in the aspects of immunological regulations. In our current project, we detected that normal rhythms were affected after inducing ICH in mice when tested on day 3 and day 10. However, after recovery, the difference in rhythmic behavior between the ICH mouse model and the control was reduced, suggesting that recovery from ICH induces correction of the circadian rhythm. We also noted that the expression levels of core clock genes in the hypothalamus were altered in the case of ICH as compared to the control. Moreover, these gene expression alterations remained the same even at day 30 of the ICH. On the other hand, the altered expression levels of two of the core clock genes (*Cry2 and Per1*) were reversed at day 10 of ICH. We are currently confirming these results and we are planning to investigate these connections by inducing ICH in clock mutant or knockout mice models. Moreover, through positron emission tomography, we have observed significant alterations in glucose uptake levels or physiological function of different brain regions of mice. The lowest glucose uptake level was found on day 3 after inducing stroke, which was increased on day 7 and remained constant until day 10. We will next study the regulation of the immune system in ICH under different light and dark schedules as well as in different clock mice models (mutant or knockout). Based on the details provided here, we suggest that for better treatment response in ICH or stroke patients, circadian rhythms should be corrected through pharmacological interventions.




**Disclosures:** **S. Khan:** None. **R. Siddique:** None.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.05/P1

**Topic:** C.09.Stroke

**Support:** Grant-in-Aid, Heart and Stroke Foundation, Canada (G-16-00012613)

**Title:** Amount of corticospinal tract affected by stroke may impact effects of transcranial direct current stimulation on upper limb reaching performance

**Authors: *J. L. CHEN**[1,3], T. K. LAM[3], M. C. BANINA[4,6], D. PISCITELLI[4,6,7], A. THIEL[5], R. H. SWARTZ[3,2], J. D. EDWARDS[8,9], R. CHEN[10], G. SCHLAUG[11], M. F. LEVIN[4,6];
[1]Fac. of Kinesiology and Physical Educ., [2]Dept. of Med. (Neurology), Sunnybrook Hlth. Sci. Ctr., Univ. of Toronto, Toronto, ON, Canada; [3]Canadian Partnership for Stroke Recovery, Hurvitz Brain Sci. Program, Sunnybrook Res. Inst., Toronto, ON, Canada; [4]Sch. of Physical and Occup. Therapy, [5]Dept. of Neurol. and Neurosurg., McGill Univ., Montreal, QC, Canada; [6]Feil/Oberfeld Res. Ctr., Jewish Rehabil. Hospital/Centre for Interdisciplinary Res. in Rehabil., Laval, QC, Canada; [7]Dept. of Kinesiology, Univ. of Conneticut, Storrs, CT; [8]Univ. of Ottawa Heart Inst., Toronto, ON, Canada; [9]Sch. of Epidemiology and Publ. Hlth., Univ. of Ottawa, Ottawa, ON, Canada; [10]Toronto Western Hosp, Krembil Res. Inst. and Univ. of Toronto, Toronto, ON, Canada; [11]Chan Med. Sch. -Baystate and Dept. of Biomed. Engin., Univ. of Massachusetts, Amherst, MA

**Abstract:** Transcranial direct current stimulation (tDCS) paired with arm training may improve post-stroke reaching performance. Previous studies applied tDCS based on the Interhemispheric Inhibition Model to inhibit an overactive contralesional motor cortex (cM1). However, evidence supporting this model is equivocal as only some individuals benefit from tDCS. A subsequent Bimodal Balance-Recovery (BBR) Model considers individual differences since cM1 overactivity may depend on the brain's residual level of structural reserve. We evaluated the BBR Model and defined structural reserve as the degree to which the corticospinal tract (CST) is preserved. A greater overlap between the stroke lesion and CST is indicative of less structural reserve (and greater motor impairment). Hypotheses: 1) participants with less CST reserve will improve reaching performance more when tDCS with the anode is applied to cM1 (A-cM1); 2) participants with more CST reserve will improve reaching performance more when tDCS with the cathode is applied to cM1 (C-cM1). We tested 25 people (sample of convenience; 22 men; mean 60.6 +/- 11.46 yrs) living with late sub-acute to chronic (> 3 mo and < 5 yr) stroke. At baseline, participants underwent magnetic resonance imaging and standardized clinical assessments. On separate days separated by two-week washout periods, participants practiced goal-directed reaching while receiving one of 3 types of tDCS (1mA 20 min, 5x7cm$^2$ electrodes in sponges): sham, A-cM1, C-cM1. Experimenters and participants were blind to study condition. Reaching performance was characterized by endpoint and joint kinematics (6 markers on trunk and arms, Optotrak Certus, 120 Hz). The primary outcome, Trunk-based Index of Performance, is a measure of skilled reaching performance incorporating endpoint speed and accuracy while accounting for compensatory trunk displacement. The secondary outcome is

trunk displacement during reaching, reflecting movement quality. Data was analyzed with linear mixed models adjusting for age and time since stroke. The amount of CST reserve did not differentially affect skilled reaching performance in response to either A-cM1 or C-cM1 ($F(1,22)=0.76$, $p=0.39$). There was a trend towards the amount of CST reserve differentially affecting trunk displacement ($F(1,21)=3.47$, $p=0.08$). Participants with less CST reserve reached with less trunk compensation when A-cM1 was applied. The same individuals used more trunk compensation when C-cM1 was applied. Findings provide modest support for the BBR model and suggest that it may be important to consider the CST reserve when deciding the type of tDCS to apply during rehabilitation.

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**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.06/P2

**Topic:** C.09.Stroke

**Support:** NIH Grant R21HD108585
NIH Grant UL1TR001436
NIH Grant TL1TR001437
Advancing Healthier WI Grant
Rev. John P. Raynor, SJ Fellowship

**Title:** Motorized intervention during split crank pedaling improves interlimb phasing, changes paretic motor output, and induces aftereffects in people with stroke

**Authors: T. RUOPP**, B. SCHMIT, *S. SCHINDLER-IVENS;
Marquette Univ., Milwaukee, WI

**Abstract:** Our prior work used split crank pedaling to identify causes of lower limb movement dysfunction after stroke (Cleland et al., 2019). We found that reduced muscle output of the paretic limb and abnormal interlimb coordination were distinct yet interrelated contributors. We suggested that rehabilitation should target both impairments and then we developed a novel intervention (i.e., CUped) to address the issue. CUped employs a motorized, split crank pedaling device. Participants are asked to pedal with both limbs while maintaining a 180° phase relationship. When the desired phasing is not achieved, motors assist the lagging limb and/or resist the leading limb until phasing is restored. This study asked whether CUped improves interlimb coordination and paretic motor output and whether effects depend on the type of motorized intervention applied: assistance (A), resistance (R), or both (AR). 19 stroke survivors were enrolled; they pedaled with each type of intervention. During pedaling, net mechanical

work (W) of the paretic limb was computed, as was the mean (μ) and standard deviation (σ) of interlimb phasing errors (E). Values were compared across interventions and to pre- and post-test conditions without intervention. Results showed that each intervention reduced μE ($p \leq 0.036$). Effects were largest for AR ($p=0.016$) and for participants with large baseline values for μE ($p<0.001$). A similar trend was observed for σE; wherein intervention decreased σE in individuals with large but not small initial values for σE ($p<0.001$). Motorized A reduced W ($p=0.002$); and motorized R increased W ($p=0.007$). The AR strategy had no significant effect on W ($p=0.079$). Changes in W were related to changes in μE ($p<0.001$). Larger reductions in μE were often associated with larger reductions in W. Increased W was sometimes associated with increased μE. When the intervention was withdrawn, improvements in μE were not sustained ($p<0.001$), and values for σE increased beyond baseline ($p<0.013$). Post hoc analysis revealed increased variation in pedaling velocity at the post-test, suggesting that participants alternated between slowing one leg and rapidly progressing the other to complete the task. We conclude that motorized intervention during split crank pedaling improves interlimb coordination post-stroke, especially when baseline deficits are marked. Intervention type has a substantial effect on paretic motor output but not interlimb coordination. Aftereffects suggest that stroke survivors can modify interlimb coordination. Training parameters should be tuned to improve interlimb coordination while promoting paretic motor output and simultaneous movement of both limbs.

**Disclosures:** **T. Ruopp:** None. **B. Schmit:** None. **S. Schindler-Ivens:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Venus Rehabilitation Technologies, LLC.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.07/P3

**Topic:** C.09.Stroke

**Title:** Activation of Sting Pathway: Implications for Learning and Memory and Stroke.

**Authors: *C. CORONA**, S. S. KARUPPAGOUNDER, Y. CHEN, I. G. CHAMBERS, R. R. RATAN;
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**Abstract:** Despite its role in protecting the brain from potentially harmful agents, converging lines of evidence seem to indicate that a sustained overstimulation of the innate immune system can disrupt the flow of information in the brain, resulting in cognitive deficits, and can negatively affect brain recovery after stroke. Studies from our lab showed that DMXAA, a specific STING (STimulator of Interferon Genes) agonist, robustly preconditioned against transient ischemia in mice by activating Interferon type-I antiviral response. Here, we hypothesize that STING plays a pivotal role in both memory formation and brain recovery after stroke. To test this hypothesis, we injected 6-8 weeks old WT mice with DMXAA (IP, 25mg/Kg)

and performed a wide variety of molecular, electrophysiological, and behavioral studies. Real-time pcr analysis revealed that STING stimulation triggered a sustained increase in Chemokine (C-C motif) ligand 5 (CCL5) expression, a protein well-known to negatively correlate with memory formation and brain recovery after stroke. Consistent with that scenario, we found that DMXAA significantly reduced hippocampal Long- Term Potentiation (LTP), an effect found absent in STING-/- mice, and hippocampus-dependent memory formation. In addition, we observed increased motor function recovery after Middle cerebral artery occlusion (MCAO) in STING-/- mice.

**Disclosures: C. Corona:** None. **S.S. Karuppagounder:** None. **Y. Chen:** None. **I.G. Chambers:** None. **R.R. Ratan:** None.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.08/P4

**Topic:** C.09.Stroke

**Support:** KAKENHI MEXT JAPAN 22K12935

**Title:** Rehabilitation Program for severely hemiparetic upper limb in chronic stroke survivors: A Case Study

**Authors: *S. MINAMI**[1], T. HORAGUCHI[2], R. KOBAYASHI[3], Y. FUKUMOTO[4], H. AOKI[5], K. MORIOKA[6], R. FUNAHASHI[7], T. KOHAMA[8], T. AOYAMA[9];
[1]Gunma Paz Univ., Takasaki, Gunma, Japan; [2]Gunma Paz Univ., Gumma, Japan; [3]Hyogo Med. Univ., Hyougo, Japan; [4]Kansai Med. Univ., Osaka, Japan; [5]Dept. Medicine, Wakayama Med. Univ., Wakayama, Japan; [6]Nagashima neurosurgery rehabilitation clinic, Osaka, Japan; [7]Rakuwakai otwa hospital, Kyoto, Japan; [8]Nkamura hospital, Osaka, Japan; [9]Dept. Medicine, Kyoto Univ., Kyoto, Japan

**Abstract:** *Introduction:* Rehabilitating severe hemiparetic upper limb in chronic stroke survivors is challenging, leading to reduced limb usage and diminished quality of life. The Purposeful Activity with Electrical Stimulation Therapy (PA-EST) program was developed to address this issue. This study investigates the relationship between changes in brain hemodynamics (measured by fNIRS) and motor function improvements through PA-EST. *Methods:* A 57s male with right hemiplegia resulting from a left capsular hemorrhage participated in the 3-month PA-EST program. Motor function was evaluated using Fugl-Meyer Assessment (FMA), goal attainment with Goal Attainment Scaling (GAS), and brain function with fNIRS. Oxyhemoglobin levels were analyzed during hand and wrist movements. *Results:* Following the PA-EST program, the participant showed improved FMA (6 to 16) and GAS-Light (25.2 to 56.2) scores, indicating enhanced motor function and adaptability. fNIRS results revealed increased Oxyhemoglobin values in the bilateral palmar area. *Conclusion:* The PA-EST program positively

influences motor function and brain hemodynamics in severe upper limb paralysis from chronic stroke. This home-based program holds promise for improving rehabilitation outcomes. Further research with a larger sample size is needed to validate these findings. *Ethics:* This study obtained approval and informed consent from participants, following the Helsinki Declaration.

**Disclosures: S. Minami:** None. **T. Horaguchi:** None. **R. Kobayashi:** None. **Y. Fukumoto:** None. **H. Aoki:** None. **K. Morioka:** None. **R. Funahashi:** None. **T. Kohama:** None. **T. Aoyama:** None.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.09/P5

**Topic:** C.09.Stroke

**Title:** Emergence of task-related spatiotemporal population dynamics in transplanted neurons

**Authors: *H. GHUMAN**, K. KIM, S. BARATI, K. GANGULY;
UCSF, San Francisco, CA

**Abstract:** Loss of nervous system tissue after severe brain injury is a main determinant of poor functional recovery. Cell transplantation is a promising method to restore lost tissue and function, yet it remains unclear if transplanted neurons can demonstrate the population level dynamics important for movement control. Here we present a comprehensive approach for long-term single neuron monitoring and manipulation of transplanted embryonic cortical neurons after cortical injury in adult mice performing a prehension task. Strikingly, the observed patterns of population activity in the transplanted network strongly resembled that of healthy networks. Specifically, the task-related spatiotemporal activity patterns of transplanted neurons could be represented by latent factors that evolve within a low dimensional manifold. We also demonstrate reliable modulation of the transplanted networks using minimally invasive epidural stimulation. Our approach will allow greater insight into how restoration of cell-type specific network dynamics *in vivo* can restore motor function.

**Disclosures: H. Ghuman:** None. **K. Kim:** None. **S. Barati:** None. **K. Ganguly:** None.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.10/P7

**Topic:** C.09.Stroke

**Support:** NIDILRR RERC COMET 90REGE0005

**Title:** The potential of error augmentation: exploring visual shifts in bimanual therapeutic training for chronic stroke survivors

**Authors:** M. VERARDI[1,2], ***C. CELIAN**[1], E. OLAVARRIA[2], F. PORTA[2], A. PEDROCCHI[3], J. L. PATTON[1,2];
[1]Shirley Ryan AbilityLab, Chicago, IL; [2]Dept. of Bioengineering, Univ. of Illinois at Chicago, Chicago, IL, USA, Univ. of Illinois at Chicago, Chicago, IL; [3]Departmento di Elettronica, Politecnico Milano, Milano, Italy

**Abstract:** Error augmentation (EA) techniques have emerged as a promising approach in bimanual therapeutic training, using both haptic forces and distorted visual displays. With the recent cost reductions for visual displays, we performed a two-arm, randomized, controlled trial where we investigated the impact of visual EA alone on clinical and kinematic performance by manipulating the cursor position of the paretic limb in the direction of error. A cohort of 38 chronic stroke survivors (post injury duration greater than 8 months) participated in a bimanual reaching exercise for approximately 40 minutes, 3 days per week, for three weeks. Both groups demonstrated an average of 2.2 improvement in Upper Extremity Fugl-Meyer ($p=0.005$, $F=5.612$), and retained it to a follow-up evaluation 7-9 weeks later (average 1.5), but did not find superiority to our EA treatment. This was not clinically meaningful, which for chronic stroke survivors is 5.2 points[1]. However, our study specifically focused on short-term effects. Our device found similar results with a composite metric that considered range of motion, asymmetry, and execution time ($p=0.031$, $F=3.70$). These findings emphasize the importance of exploring non-pharmacological interventions for stroke recovery and advancing the understanding of error augmentation techniques in neurorehabilitation.
[1]Page SJ, Fulk GD, Boyne P. Clinically important differences for the upper-extremity Fugl-Meyer Scale in people with minimal to moderate impairment due to chronic stroke. Phys Ther. 2012;92(6):791-798.

**Disclosures: M. Verardi:** None. **C. Celian:** None. **E. Olavarria:** None. **F. Porta:** None. **A. Pedrocchi:** None. **J.L. Patton:** None.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.11/P8

**Topic:** C.09.Stroke

**Support:** NRF-2019M3C1B8090841
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NRF-2023R1A2C3002798

**Title:** Astrocytic OptoSTIM1 stimulation of astrocyte enhance post-stroke recovery in chronic capsular infarct model

**Authors: J. CHO**[1], S. LEE[2], J. PARK[1], W. HEO[3], C. LEE[2], *H.-I. KIM[1];
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**Abstract:** The emphasis on neuronal mechanism in post-stroke recovery has been well-established, particularly through the process of synaptic plasticity. However, it is now recognized that astrocyte, traditionally viewed as supportive cells, have a more complex role in brain functions, including their ability to influence synaptic remodeling. To fully understand the unique contribution of astrocytes in stroke recovery, it is crucial to selectively activate these cells and investigate their underlying mechanisms. Nonetheless, there is ongoing controversy regarding the selective activation of astrocyte and their actual contribution to promoting functional recovery in stroke models. In this study, we employed an optogenetic stimulation technique using viral vectors including Lenti-GFAP-ChR2-eYFP (ChR2 Stim. Group: CSG) to manipulate astrocyte ion channels and Lenti-GFAP-OptoSTIM1-eYFP (OptoSTIM1 Stim.Group: OSG) to directly activate $Ca^{2+}$ release-activated $Ca^{2+}$ (CRAC) channels. Following two weeks of astrocytic stimulation in the ipsilesional sensori-parietal cortex, OSG showed a significant functional recovery in chronic capsular infarct, whereas CSG demonstrated no recovery. Longitudinal 2-deoxy-2-[18F]-fluoro-D-glucose microPET (FDG-microPET) imaging showed a significant reduction in cortical diaschisis volume in OSG, which correlated with motor recovery. FDG-microPET also showed an activation of corticocortical circuit, presumed to be responsible for functional recovery. Furthermore. The OSG demonstrate an increased expression of c-Fos and brain derived neurotrophic factor (BDNF) in both neurons and astrocytes, indicating a potential interaction between neurons and astrocyte, ultimately leading to increase the brain plasticity. These findings indicate that astrocytic activation through endogenous calcium elevation using OptoSTIM1 can be considered as a therapeutic option to enhance post-stroke recovery in capsular infarct.

**Disclosures: J. Cho:** None. **S. Lee:** None. **J. Park:** None. **W. Heo:** None. **C. Lee:** None. **H. Kim:** None.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.12/P9

**Topic:** C.09.Stroke

**Support:** IITP-2023-2020-0-01821
RS-2023-00208884

**Title:** Differences in Factors Influencing Responsiveness to Combined Intervention of Robot-assisted Gait Training and Noninvasive Brain Simulation in Stroke Patients - Neuroimaging Study

**Authors: *J. LEE**[1], E. KIM[2], Y.-H. KIM[2];
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**Abstract:** Gait ability in stroke patients is associated with their activities of daily living and quality of life. To achieve satisfactory improvement of gait ability in stroke patients, the simultaneous intervention of robot-assisted gait training (RAGT) and transcranial direct current stimulation (tDCS) was suggested. However, the effectiveness of combined RAGT and tDCS intervention was varied according to previous studies. This study was conducted to investigate differences in patient characteristics between good and poor responders of combined RAGT and high-definition transcranial direct current stimulation (HD-tDCS) intervention through neuroimaging-based subgroup analysis. Twenty-four chronic stroke patients participated in this study. The subjects were randomly allocated to either the experimental group (RAGT with real HD-tDCS) or the control group (RAGT with sham HD-tDCS). All participants completed 10 sessions over four consecutive weeks. Participants were classified into good and poor responder groups based on gait speed improvement after the intervention. Neuroimaging measures, including fractional anisotropy (FA) values of the corticospinal tract (CST) and corona radiata (CR) and network efficiency and network density of the functional network, were obtained from neuroimaging data, including diffusion tensor imaging, resting-state functional MRI, at pre-intervention. The CST and CR FA values and network efficiency were higher in the good responder group compared to the poor responder group in the experimental group. In contrast, these values did not show a significant difference between good and poor responder groups in the control group. This study result can be used to decide candidates among chronic stroke patients for receiving combined RAGT and tDCS intervention and will contribute to increasing the clinical value of the combined intervention.

**Disclosures: J. Lee:** None. **E. Kim:** None. **Y. Kim:** None.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.13/P10

**Topic:** C.09.Stroke

**Title:** Short-term BCI intervention in chronic stroke induces motor improvements through changes in functional connectivity

**Authors: *K. A. GRIGORYAN**[1], K. MÜLLER[2], M. WAGNER[1], D. MASRI[1], A. VILLRINGER[1,3], B. SEHM[1,4];

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**Abstract:** Stroke is a prevalent source of motor impairment worldwide. While survivors experience some level of spontaneous motor function recovery during the acute phase, the progress may plateau. Emerging evidence suggests that brain-computer interface (BCI)-based rehabilitation therapies may surpass this plateau by fostering neuroplasticity and functional recovery (Cervera et al., 2018; Mansour et al., 2022). Motivated by these findings, the present study aims to investigate the underlying neurophysiological mechanisms of BCI-driven post-stroke rehabilitation by recruiting a cohort of 21 chronic stroke patients (5 females, age: 60.8 ± 8.7, time since stroke in months: 53.8 ± 44.5), randomized into experimental (n = 11) and control groups (n = 10) in a longitudinal crossover design with delayed start. Both groups underwent a 6-day BCI training and were assessed pre- and post-training using the Fugl-Meyer Upper Extremity (FM-UE) clinical scale of motor impairment. The BCI training consisted of wrist dorsiflexion motor imagery while receiving visual and tactile feedback. All participants underwent baseline, pre- and post-training, and follow-up functional and structural MRI scans. The rs-fMRI data was preprocessed using CONN toolbox (Whitfield-Gabrieli et al., 2012). Seed-based connectivity maps were estimated using denoised and bandpass filtered data (four seed regions of default mode network (DMN), defined from CONN toolbox's ICA analyses of HCP dataset). To evaluate the group effect of the intervention, we constructed and fitted the flexible-factorial model. Recent studies have demonstrated that stroke can disrupt the DMN, leading to changes in brain connectivity and function that contribute to post-stroke motor deficits (Cassidy et al., 2022; Olafson et al., 2022). Our findings revealed an increase in connectivity between the medial prefrontal cortex (mPFC) of DMN (seed 001), and the premotor, superior parietal cortices and SMA. Notably, we found that the FMA-UE significantly correlated with the increase in connectivity between the mPFC, and M1 and premotor cortex.In the behavioral domain, participants learned operating the BCI, with the greatest improvement in accuracy on the second day. Importantly, the 6-day training resulted in improvement in upper limb motor function as assessed by FMA-UE. Our results suggest that even a short-term BCI intervention induces a clinically relevant improvement in motor function in chronic stroke. The underlying mechanisms involve neuroplastic changes in functional connectivity between DMN and motor-related areas.

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**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.14/Q1

**Topic:** C.09.Stroke

**Support:** This research was supported by the Rhode Island Institutional Development Award (IDeA) Network of Biomedical Research Excellence from the National Institutes of Health under grant number P20GM103430

**Title:** Development of a novel seamless magnetic-based actuated planar robotic platform for upper limb extremity rehabilitation

**Authors: *S. GHAFOORI**[1], K. WELLINGTON[1], B. GARNEAU[1], A. KONING[1], E. BROADMEADOW[1], M. NOROUZI[1], M. JOUANEH[2], Y. SHAHRIARI[3], R. ABIRI[1]; [1]Electrical, Computer, and Biomed. Engin., [2]Mechanical Engin., Univ. of Rhode Island, Kingston, RI; [3]Electrical, Computer, and Biomed. Engin., Univ. of Rhode Island, West Kingston, RI

**Abstract:** Stroke is one of the leading causes of death and individuals surviving from it mostly tackle upper-limb motor control. Therefore, the rehabilitation platforms such as planar robotics have been designed to mitigate the problem and assist patients through upper-limb extremity (reach-return) training. However, regarding user interface and mechanical motion, such rehabilitation platforms (e.g. with belt-based mechanism) lack proper smoothness and transferability of the driver mechanism. Here, we introduced a magnetic-based driver mechanism as a novel technique to transfer the force between the planar robot and human wrist hand in a seamless way for extremity training. This technology will not only improve the usability of the overall system but also provide a lock/unlock mechanism for the patient's hand through a controllable magnetic force field (e.g. electromagnetic strategy). To test the achievability of our theory and mechanism, we designed a one-dimensional planar robotic device embedded with magnetic actuators for exercising shoulder movements horizontally. We observed that the motion from our motor-driven mechanism can smoothly transfer from a permanent magnet as the "driver" to another permanent magnet as the "follower". The driver and follower were separated by plexiglass for improving the user interface. For investigating the characterization of the static and dynamic behavior of the overall system, we had the bottom magnet stay still, and horizontal forces about 15 Newton caused instant detachment. Whereas the same amount of vertical force did not lead to disengagement when the bottom magnet was moving with 20 RPM of motor speed, and offset was maintained around 3 centimeters. However, that was when the human hand was not involved. Therefore, we developed a closed-loop online Extended Kalman Filter (EKF) algorithm to estimate the offset between the positions of the magnets and then prevent detachment by regulating the driver magnet's speed using an PID controller. Overall, our system demonstrated promising results and a more improved human-machine interaction experience in planar robotic platforms.

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**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.15/Q2

**Topic:** C.09.Stroke

**Title:** Effects of social competition on motor rehabilitative training efficacy after motor cortical infarcts in rats

**Authors: *M. FRACASSI**[1], T. A. JONES[2];
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**Abstract:** Motor rehabilitation can improve upper limb impairment following stroke but there is often considerable room for further improvement. Motivation to engage in rehabilitative training can contribute to the magnitude of its success. Previous studies have indicated that a socially enriched environment and social interactions have positive effects on functional recovery after an ischemic stroke. Here we investigated the possibility that social competition in the performance of motor rehabilitative training could enhance its efficacy in improving forelimb function. This was tested in a rat model of chronic post-stroke upper limb impairments resulting from ischemic infarcts of primary motor cortex.
Forty-three socially housed male Long Evans rats underwent pre-stroke training to establish a skilled reaching task, followed by infarct induction, and rehabilitative training in skilled reaching. During the pre-stroke training phase, the rats learned the single pellet retrieval task, in which they reach through a narrow window to retrieve individual banana-flavored food pellets. Their social hierarchy status was also determined. Subsequently, stroke was induced by topically applying endothelin-1 to the caudal forelimb area of motor cortex opposite their trained forelimb. The animals were then divided into two groups: a social competitive group and an individual training group. In the competitive group, pairs of rats were trained in chambers facing each other to reach for the same pellet at the same time, i.e., they competed to retrieve individual food rewards. Both groups underwent daily rehabilitative training for four weeks.
Rats had similar success rates in the reaching task before and immediately after the stroke. However, during the four-week rehabilitative training period, dominant rats in the social competitive group exhibited significantly higher success rates per reach attempt compared to the individual training group. Subordinate rats of the competitive group performed similarly to those of the individual training group. Analysis of lesion volume and extent in Nissl-stained sections did not reveal any differences between the groups. These findings demonstrate the beneficial impact of social competition in dominant rats during motor rehabilitation and underscore the potential influence of social hierarchy on post-stroke recovery in social settings.

**Disclosures: M. Fracassi:** None. **T.A. Jones:** None.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.16/Q3

**Topic:** C.09.Stroke

**Support:** the Translational R&D Program on Smart Rehabilitation Exercises (#TRSRE PS01), National Rehabilitation Center, Ministry of Health and Welfare, Korea

**Title:** The clinical effects and feasibility of moderate-to-high intensity exercise program for stroke survivors

**Authors: *S. JUNG**[1,2];
[1]Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of; [2]Rehabil. Med., Seoul Natl. Univ. Boramae Med. Ctr., Seoul, Korea, Republic of

**Abstract:** Background: Post-stroke exercise need to be encouraged to facilitate optimal recovery and to improve both physical and mental health. However, stroke survivors are easily predisposed to sedentary lifestyle due to physical impairment and functional compromise. Moreover, many clinicians as well as patients tend to be discouraged by exercise-related risk of injury of falls or comorbidities.
Methods: This study is a randomized controlled trial. Subjects were randomly assigned to either intervention or control group. Subjects in intervention group completed 16 sessions of 90-minute moderate-to-high intensity group-based exercise for 8 weeks. Isometric muscle strength and grip strength of the affected and unaffected side, 10 repetition sit-to-stand test (STS10), 60 second sit-to-stand test (STS60), Short Physical Performance Battery (SPPB), multidirectional reach test, Berg's Balance scale (BBS), 10-meter walk test, 6 minute walk test, Timed-up-and-go test, physiological cost index, Korean version of modified Barthel index, Fugl-Myer Assessment (FMA) and Korean version of Montreal Cognitive Assessment (MoCA-K) were measured at baseline and postintervention. Bone density and body composition were analyzed by dual energy X-ray absorptiometry (DEXA) at baseline and postintervention.
Results: Total 32 stroke survivors were enrolled in the study and 18 were randomized to group-based moderate-to-high exercise and 14 were randomized to home-based low intensity exercise. Intervention group showed high compliance as well as high attendance rate. Adverse event was only 2 uneventful falls in 1 subject. After 8 weeks of moderate-to-high intensity group exercise, subjects showed significant improvement in isometric muscle strength of hip extensors and knee flexors and grip strength both in affected and unaffected limbs, and isometric muscle strength of affected shoulder abductor. Also, STS60, SPPB, BBS, FMA and MoCA-K were significantly improved in the intervention group after 8-week of moderate-to-high intensity exercise. Femur bone density and lean mass improved after the exercise in group exercise subjects.
Conclusions: Moderate-to-high intensity group-based exercise is feasible and safe and improves physical and cognitive function of chronic stroke survivors.

**Disclosures: S. Jung:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; the Translational R&D Program on Smart Rehabilitation Exercises (#TRSRE PS01), National Rehabilitation Center, Ministry of Health and Welfare, Korea.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.17/Q4

**Topic:** C.09.Stroke

**Support:** NIH Grant R01HD075777

**Title:** The effect of transcranial direct current stimulation (tDCS) combined with high-intensity speed-based treadmill training on ankle motor control in chronic stroke survivors.

**Authors: *A. DOSHI**[1], A. CHANDHOK[3], S. MADHAVAN[2];
[1]Neurosci., [2]Physical Therapy, Univ. of Illinois At Chicago, Chicago, IL; [3]Univ. of Illinois Chicago, Chicago, IL

**Abstract: Background:** Gait impairments and diminished ankle motor control are prevalent among stroke survivors, resulting in a long-term decrease in quality of life. Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that has been demonstrated to prime motor learning and performance in stroke survivors. High intensity interval training (HIIT) is an effective form of gait rehabilitation for improving gait speed. Speed-based HIIT (HISTT) yields greater gains in power and fatigue resistance compared to classic HIIT. However, there remains a gap in the combined effect of tDCS with HISTT on ankle motor control in stroke survivors. Additionally, the association between ankle motor control and treadmill belt speed during HISTT has not been studied Exploring the potential synergistic benefits of these interventions could provide valuable insights into enhancing gait rehabilitation outcomes for this population.
**Objective:** The purpose of the study is to evaluate the potential benefits of combining tDCS with HISTT on ankle motor control in chronic stroke survivors. We also aim to determine the association of ankle motor control with treadmill belt speed.
**Methods:** Data were collected as a part of a larger clinical trial where participants with chronic stroke performed 12 sessions of HISTT, which involved alternating periods of walking at the maximum tolerated treadmill speed and recovery speed. Participants were randomly assigned to one of two groups: tDCS + HISTT (n = 6) and HISTT (n = 6). The HISTT group received 40-minute sessions of high-intensity speed-based treadmill training over a period of 4 weeks (3 sessions/week), while the tDCS + HISTT group received anodal tDCS prior to the HISTT during each session. To measure ankle motor control, participants performed ankle plantarflexion and dorsiflexion movements while tracking a sinusoidal target. Spatiotemporal error was calculated between the ankle position and target.
**Results:** Spatiotemporal error was significant lower in the tDCS + HISTT group compared to the HISTT group ($t = -2.6797$, $p < 0.05$). The tDCS + HISTT group showed greater improvement (7.8%) on the ankle motor tracking task after 12 sessions (mean = 0.19) compared to the HISTT group (mean = 0.22). The treadmill belt speed had a significant positive effect ankle spatiotemporal error with an estimated coefficient of 0.095387 ($p < 0.01$). The results indicated a weak relationship between the two variables ($R^2_{Adj} = 0.04362$, $F = 7.522$, $p < 0.01$).
**Discussion:** Our results suggest that combining HISTT with tDCS could result in improved

ankle motor control in chronic stroke survivors, surpassing the benefits observed with HISTT alone.

**Disclosures:** **A. Doshi:** None. **A. Chandhok:** None. **S. Madhavan:** None.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.18/Q5

**Topic:** C.09.Stroke

**Support:** Craig H. Nielsen Foundation 649297
University of Pittsburgh Internal Funding

**Title:** GABA increases primary afferent input in spinal and cortical sensorimotor circuits in monkeys

**Authors: *L. LIANG**[1], A. A. MAHROUS[5], J. BALAGUER[2], J. C. HO[3], E. M. GRIGSBY[1], V. KARAPETYAN[3], A. DAMIANI[3], D. P. FIELDS[3], P. GERSZTEN[3], J. A. GONZÁLEZ-MARTÍNEZ[4], D. J. BENNETT[7], C. J. HECKMAN[6], M. CAPOGROSSO[3], E. PIRONDINI[2]; [2]Rehab Neural Engin. Labs, [3]Univ. of Pittsburgh, [4]Univ. of Pittburgh, [1]Univ. of Pittsburgh, Pittsburgh, PA; [5]Northwestern Univ., Northwestern Univ., Chicago, IL; [6]Northwestern Univ., Oak Park, IL; [7]Univ. Of Alberta, Univ. of Alberta, Edmonton, AB, Canada

**Abstract:** Primary afferent depolarization (PAD) mediated by $GABA_A$ receptors was believed to modulate sensory flow by inhibiting sensory axons in the spinal cord to sculpt neural inputs into skilled motor output. Recent studies in rodents revealed that these $GABA_A$ receptors reside at afferent branching points, and PAD prevents action potential failures, challenging its long believed inhibitory role on sensory transmission. While PAD is pertinent to fine motor control, most experimental data came from animal models that lack sophisticated neural circuits to support skilled motor control. Here, we investigated the controversial role of PAD on sensory gating directly in the monkey cervical spinal cord through observing sensory evoked spinal activity, motor output, and supraspinal field potentials.

We used an acute setup in anesthetized monkeys (n=3) to stimulate sensory afferents and record along the sensorimotor pathway. We placed a bipolar nerve cuff on the deep radial nerve and a bipolar stimulation probe on dorsal rootlets (C6-T1) to activate primary afferents. We recorded PAD in a distally severed dorsal rootlet with a silver hook electrode, electromyography (EMG) from arm and hand muscles, intraspinal activity from the C5/C6 spinal cord with a linear microelectrode array (32 Ch) placed dorsoventrally throughout the spinal laminae, as well as thalamic and sensory cortex (S1) field potentials with a deep brain electrode and an intracortical array, respectively.

To evaluate the function of PAD, we first stimulated the afferents with single, doublet, and burst pulses. Then, we intrathecally applied bicuculline, a $GABA_A$ inverse agonist, to remove PAD,

and repeated the experiments. In the dorsal spinal cord, we observed minimal change in the afferent volley, but PAD peak amplitude significantly reduced after bicuculline, confirming that PAD is mediated by $GABA_A$ in spinal gray matter in monkeys. Further, we found an overall increase in spinal spontaneous firing after bicuculline, while in contrast, sensory input related units decreased in firing, indicating a sensory specific facilitation by PAD. In addition, single pulse evoked EMG responses were significantly suppressed after bicuculine, and interestingly, multi-pulse stimulation exhibited increased response failures to subsequent pulses. Finally, sensory evoked field potentials in the thalamus and S1 were also significantly suppressed after bicuculline. Our results in monkeys support the facilitatory role of GABA on sensory transmission, which can increase spinal and cortical neural responses to sensory inputs, changing our understanding of generation and perception of movement.

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**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.19/Q6

**Topic:** C.09.Stroke

**Title:** Investigating Cold Spreading Depolarization (cold-SD) in Rodent Brain Slices

**Authors: *D. A. HANCOCK**, E. R. N. KIARIE, P. J. GAGOLEWICZ, R. D. ANDREW; Queen's Univ., Kingston, ON, Canada

**Abstract:** Neuronal damage induced by mild hypothermia (<15°C) was first demonstrated in non-hibernating mammals where cold temperatures caused cerebral edema, with an associated accumulation of Na+ intracellularly and K+ extracellularly (Thauer & Brendel, 1962). As well, a so-called ‘chill coma’ has been documented in insects (locusts, fruit flies) when they are exposed to near-freezing (n/f) temperatures, evoking spreading depolarization (SD) (Robertson et al., 2020). We propose that, surprisingly, exposure to n/f temperature causes an SD-like event in mammalian higher brain, which we term `cold SD`. SD is a mass wave of propagating cellular depolarization caused by failure of the Na+/K+ pump particularly in neurons. SD during ischemia causes cell swelling, neuronal injury, and death as during stroke, traumatic brain injury, and sudden cardiac arrest. We hypothesize that cold-SD can be caused by compromised Na+/K+ pump function due to reduced ATP production at n/f temperatures. This study builds on research that shows neuronal swelling and dendritic beading in rodent slices upon cooling to ~6°C (Kirov et al., 2004) and on our previous lab findings that n/f temperature (3-6°C) evokes cold SD in rodent slices, observable by imaging changes in light transmittance (LT). As bath temperature dropped from 10oC to 3-6°C over 200 to 300 seconds, LT decreased in neocortex coinciding

with a slow positive drift in extracellular voltage of 2-3 mV recorded with a KCl pipette. Then, when SD initiation was imaged, a negative DC shift of 2 to 4 mV coincided with the front passing the pipette, so this is a classic SD event with a slower propagation and reduced peak cell swelling as compared to OGD-SD. As well, slices that underwent cold SD when slowly warmed could generate OGD-SD, demonstrating clear recoverability from cold-SD. The TRPM8 receptor is involved with cold reception, but its specific antagonist PBMC (25nM) did not affect cold SD parameters. We conclude that 1) the standard technique of preparing rodent slices at n/f temperatures often induces cold SD from which slices recover upon warming; 2) Surprisingly, energy to drive cold-SD is maintained even in n/f mammalian gray matter because the Gibbs-Donnan equilibrium remains intact by Na+/K+ ATPase transport. The pump maintains the chemical and electrical energy differential between the intra- and extracellular compartments. So, while heat can be pulled from the tissue by lowering temperature, SD can still be generated so long as the pump functions. 3) Although non-hibernating mammals cannot survive n/f temperatures due to systemic failure, certain bat species likely undergo cold SD and survive in the real world, much like insects.

**Disclosures: D.A. Hancock:** None. **E.R.N. Kiarie:** None. **P.J. Gagolewicz:** None. **R.D. Andrew:** None.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.20/Q7

**Topic:** C.09.Stroke

**Support:** MOH-000207
MOH-000212
Duke-NUS-KPFA/2021/0047

**Title:** Enabling the Survival of Transplanted Neural Progenitors and Reconstructing the Corticospinal Tract in Stroke

**Authors: *Z. WANG**[1], D. ZHENG[2];
[1]NBD, Duke-National Univ. of Singapore, Singapore, Singapore; [2]Duke-Nus Grad. Med. Sch. Singapore, Duke-Nus Grad. Med. Sch. Singapore, Singapore, Singapore

**Abstract:** Stroke is the second leading cause of death and third leading cause of disability globally. It is caused by cerebral hypoxia that quickly results in irreversible neuronal injury. The main therapeutic options are confined to reperfusion therapy at the acute phase, and there are no effective therapeutic options after that. Stem cell therapies potentially protect the host neurons from further damage and/or replace the lost neurons. However, this strategy is hindered by the poor survival of the neural precursor cells (NPCs) transplanted into the inflammatory ischemic core. Here we develop a chemical cocktail consisting of fibrinogen and maraviroc to promote the

survival of the transplanted NPCs in the ischemic core of the mouse cerebral cortex. This is achieved by blocking the activation of CCR5 on the NPCs, thus protecting the NPCs from apoptosis induced by pro-inflammatory factors. The surviving NPCs divide and differentiate to mature neurons within 2-4 weeks, filling the infarct region with vascularization and reduced gliosis. Over time, the transplanted cortical neurons grow out axons and undergo long-distance growth from the cortex to the brainstem and spinal cord, reconstructing the corticospinal tract and correcting the motor deficits of the grafted mice. Our cocktail enables the survival of the transplanted NPCs in inflammatory neurological conditions like stroke. Our findings highlight the prospect of reconstructing neural circuits through long-distance axonal growth by transplanted human NPCs.

**Disclosures: Z. Wang:** None. **D. Zheng:** None.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.21/Q8

**Topic:** C.09.Stroke

**Support:** NRF research program 2021R1A2C2006110
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**Title:** Detrimental role of Arginase-1 expressing infiltrating macrophages in post-stroke inflammatory environment and functional recovery

**Authors: *H. KIM**[1,2], H. PARK[1,2], Y. SEO[1,2], S. GENISCAN[1,2], Y. OH[1,2], B. KIM[1,2,3]; [1]Ajou Univ. Sch. of Med., Suwon, Korea, Republic of; [2]Dept. of Biomed. Sci., Neurosci. Grad. Program, Ajou Univ. Grad. Sch. of Med., Suwon, Korea, Republic of; [3]Dept. of Neurol., Ajou Univ. Sch. of Medicine., Suwon, Korea, Republic of

**Abstract:** Ischemic stroke induces immoderate inflammatory responses that cause secondary damage to the tissue. This inflammatory process involves both CNS resident microglia and peripherally derived macrophages. Arginase-1 (Arg1), an anti-inflammatory marker of polarized immune cells, has the potential to modulate the post-stroke inflammatory microenvironment. However, the specific role of Arg1 following ischemic stroke remains unclear. Therefore, this study aimed to investigate the functional role of Arg1 in mice with photothrombotic ischemic stroke. The expression of Arg1 significantly increased at the border of the lesion core in a time-dependent manner. Immunohistochemistry analysis revealed that the majority of Arg1 expressed in Iba-1 positive immune cells. In addition, Arg1 expression was predominantly observed in infiltrating macrophages marked by LysM+ in LysM-Cre::Rosa26-eYFP mice, rather than in CX3CR1+ microglia in CX3CR1-GFP mice. This suggests that infiltrating macrophages express

Arg1 following ischemic stroke. To assess the functional role of Arg1 in post-stroke recovery, LysM-cre::$Arg1^{fl/fl}$ conditional knockout (Arg1 cKO) mice were generated. Remarkably, motor functional behavior tests conducted for up to 4 weeks post-stroke revealed improved functional recovery of forelimb use and skilled walking in Arg1 cKO mice. These findings suggest that Arg1 may have detrimental effects on functional recovery after ischemic stroke. Histological analysis showed that Arg1 cKO mice had reduced levels of fibronectin and chondroitin sulfate proteoglycans (CSPGs, CS56), indicating a potential role for Arg1 in regulating post-stroke fibrotic scar development. Furthermore, decreased levels of peri-neuronal nets were observed in the peri-infarct region of Arg1 cKO mice. Interestingly, Arg1 cKO mice displayed a significantly higher number of excitatory synapses in the peri-infarct area. To further elucidate the underlying microenvironmental changes in Arg1 cKO mice after stroke, cytokine profiles of peri-infarct microglia were analyzed at 7 days after stroke. The analysis revealed a decrease in TGF-beta signaling and pro-inflammatory cytokines in Arg1 cKO mice. Additionally, expression of microglial phagocytic markers was decreased. Together, these findings suggest that infiltrating macrophages expressing Arg1 may regulate the development of fibrosis and pro-inflammatory microglial environment. Currently, we are evaluating the potential cross-talk between Arg1-expressing macrophages and microglia involved in post-stroke inflammation and recovery.

**Disclosures: H. Kim:** None. **H. Park:** None. **Y. Seo:** None. **S. Geniscan:** None. **Y. Oh:** None. **B. Kim:** None.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.22/R1

**Topic:** C.09.Stroke

**Support:** American Heart Association Postdoctoral Fellowship 897715
Cleveland Clinic Imaging Sciences Pilot Study Grant
Cleveland Clinic Research Program Committees (RPC) Grant 4564
NIH Grant R01HD098073

**Title:** A novel brain stimulation approach to promote bimanual motor function and control in chronic stroke - a pilot clinical study

**Authors: *X. LI**[1], J. KNUTSON[2,3], D. CUNNINGHAM[2,3], M. LOWE[4], E. BARDEN[1,5], T. BENNETT[1], K. O'LAUGHLIN[1], M. WIDINA[1], E. PLOW[1,6,7];
[1]Biomed. Engin., Cleveland Clin. Lerner Res. Inst., Cleveland, OH; [2]Physical Med. and Rehabil., MetroHealth Rehabil. Inst., Cleveland, OH; [3]Physical Med. and Rehabil., Case Western Reserve Univ., Cleveland, OH; [4]Diagnos. Radiology, Cleveland Clin. Imaging Inst., Cleveland, OH; [6]Physical Med. and Rehabil., [5]Cleveland Clin. Neurolog. Inst., Cleveland, OH; [7]Cleveland Clin. Rehabil. Hosp., Cleveland, OH

**Abstract:** The majority of stroke survivors have chronic upper limb paresis that limits their ability to perform daily tasks. Most daily tasks require bimanual arm and hand use. Superior bimanual function is associated with better functional independence in stroke. Yet, stroke rehabilitation research and interventions generally focus on promoting unimanual gains. Unfortunately, unimanual gains do not fully transfer to improved bimanual abilities. In this study, we are testing the hypothesis that non-invasive brain stimulation delivered to contralesional higher motor cortices (cHMC) using repetitive transcranial magnetic stimulation (rTMS) combined with bimanual motor training will lead to favorable effects on bimanual motor function and control in chronic stroke survivors. CHMC are anatomically specialized to control bimanual movement given their dense interhemispheric, crossed and uncrossed connections. Our ongoing triple-blinded pilot randomized controlled study will estimate the effects of delivering multiple sessions of cHMC rTMS in combination with bimanual rehabilitation in persons with chronic stroke. Participants 18-90 years of age who are >6 months post unilateral ischemic or hemorrhagic stroke are included. Individuals are required to have ≥10º wrist, finger and thumb extension but score ≤11/14 points on the hand section of upper extremity Fugl-Meyer (UEFM). Participants are randomized to receive cHMC rTMS or sham rTMS immediately preceding rehabilitation 2x/week for 6 weeks. Rehabilitation consists of 100% bimanual functional task practice. Assessments of bimanual motor function and control, neurophysiology and resting-state functional connectivity are made twice at baseline and repeated at end-of-treatment. Motor function and control tests are also repeated at 1-month follow-up. Nine participants have completed baseline testing so far. Of the 7 participants who completed post-test, bimanual motor function measured with Bimanual Assessment Measure (BAM) increased from 83.6 ± 5.9 (mean ± SD) to 88.7 ± 3.7, while unimanual motor impairment scores (UEFM) improved slightly (43.1 ± 8.5 to 45.1 ± 10.1). This may indicate bimanual training specifically improves bimanual function. Paretic force contribution in bimanual motor control test also increased from 31.7% ± 8.8% to 36.7% ± 4.5% (typically 50% in healthy individuals), indicating more involvement of the paretic hand in bimanual force control. Enrollment will end September 2023 and group results (anticipated n=14) will be presented. Effect size estimates will be generated to determine sample sizes for future investigation of bimanual function in stroke.

**Disclosures:** **X. Li:** None. **J. Knutson:** None. **D. Cunningham:** None. **M. Lowe:** None. **E. Barden:** None. **T. Bennett:** None. **K. O'Laughlin:** None. **M. Widina:** None. **E. Plow:** None.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.23/R2

**Topic:** C.09.Stroke

**Title:** Intraperitoneal, but not intracerebroventricular, IGF1 treatment repairs ischemic stroke-induced acute gut damage and improves cognitive behaviors in acyclic middle-aged female rats

**Authors: *K. MANI**;
Texas A & M Univ., Bryan, TX

**Abstract:** Stroke is the leading cause of long-term disability and a risk factor for dementia. Hence stroke therapies are urgently needed to improve the quality of life for stroke survivors, especially women who are at a greater risk for stroke after menopause. Our previous studies have modeled this population using acyclic middle-aged female rats. This group has lower circulating levels of the peptide hormone Insulin-like Growth Factor (IGF1) and display worse outcomes after a stroke than young adult female rats. ICV administration of IGF1 to this group decreases infarct volume, improves sensory motor performance and reduces cytokine levels in the ischemic hemisphere. Despite this neuroprotection, icv IGF1 treatment did not reduce peripheral inflammation or improve cognitive in the chronic phase of stroke. In view of the evidence that stroke induces gut dysbiosis, and that gut dysfunction is implicated in cognitive behaviors, we hypothesize that, unlike icv IGF1 treatment, which is restricted to the brain, systemic (ip) IGF1 treatment would repair the gut, attenuate peripheral cytokine levels and improve long-term behavior outcomes. Acylic middle-aged Sprague Dawley female rats (9-11 mos) were subjected to endothelin-1 induced middle cerebral artery occlusion (MCAo) or sham operation. Animals received ip IGF1 injections 4h and 24h post MCAo, or icv infusions, while controls received vehicle. Sensory motor tests, blood and gut samples were acquired pre and post MCAo. Animals were terminated either in the acute phase (2d) or chronic phase (30d). The latter group was also subject to tests of cognition. In contrast to icv treatment, ip-IGF1 did not reduce infarct volume or acute sensory motor impairment but significantly attenuated circulating levels of IL-6 and IL-17 and attenuated the post stroke cognitive deficits as assessed by the Barnes Maze assay and Novel Object Recognition Test. IP-IGF-1 reduced post stroke gut dysmorphology, by preserving villus:crypt ratio and attenuating crypt hyperplasia in the acute phase and resulted in preservation of the major phyla of the gut microbiome in the chronic phase, as well as the abundance of the lactobacillus family which has been shown to produce neuroprotective short chain fatty acids. Our data suggest that systemic IGF1 may be a better therapeutic option for long term cognitive behaviors after stroke.

**Disclosures: K. Mani:** None.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.24/R3

**Topic:** C.09.Stroke

**Support:** Cell Prothera

**Title:** Multiple routes of delivery of CD+34 stem cells reduce stroke symptoms via extracellular vesicle-mediated neurogenesis and angiogenesis

**Authors:** J.-Y. LEE[1], C. VIGNON[2], H. STREEFKERK[2], M. DE KALBERMATTEN[2], I. GARITAONANDIA[2], ***C. BORLONGAN**[3];
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**Abstract:** Stroke remains a major cause of death in the United States and around the world. Survivors are left with debilitating motor and neurological deficits. The limited treatment options indicate finding novel strategies for stroke. Stem cell-based therapy stands as an experimental treatment for stroke. However, clinical trials of stem cell transplantation in stroke has mostly demonstrated safety and not efficacy likely due to lab-to-clinic translational hurdles. Here, we performed vis-a-vis comparison of different routes of transplantation, namely intracerebral, intraarterial, and intranasal delivery of expanded human CD34+ stem cells, called ProtheraCytes®, in the established stroke model of transient middle cerebral artery occlusion (MCAO) using adult Sprague-Dawley rats. Following optimization of the dose and subacute timing of cell delivery, animals were randomly assigned to receive either ProtheraCytes® or vehicle. Motor and neurological assays from day 7 to day 28 post-stroke revealed significant functional recovery across all three delivery routes of ProtheraCytes® compared to vehicle-treated stroke rats. Additionally, ProtheraCytes®-transplanted stroke rats displayed significantly reduced infarct size and cell loss in the peri-infarct area coupled with enhanced neurogenesis and angiogenesis compared to vehicle-treated stroke rats. Mechanistically, ProtheraCytes® may secrete extracellular vesicles, in particular CD-63, which appear to be associated with the observed upregulation of neurogenesis and angiogenesis. These findings support the safety and efficacy of transplanting ProtheraCytes®, including via the minimally invasive intranasal route, in affording robust and stable behavioral and histological therapeutic effects in an animal model of stroke.

**Disclosures: J. Lee:** None. **C. Vignon:** A. Employment/Salary (full or part-time); Cell Prothera. **H. Streefkerk:** A. Employment/Salary (full or part-time); Cell Prothera. **M. de Kalbermatten:** A. Employment/Salary (full or part-time); Cell Prothera. **I. Garitaonandia:** A. Employment/Salary (full or part-time); Cell Prothera. **C. Borlongan:** A. Employment/Salary (full or part-time); University of South Florida. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Cell Prothera.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

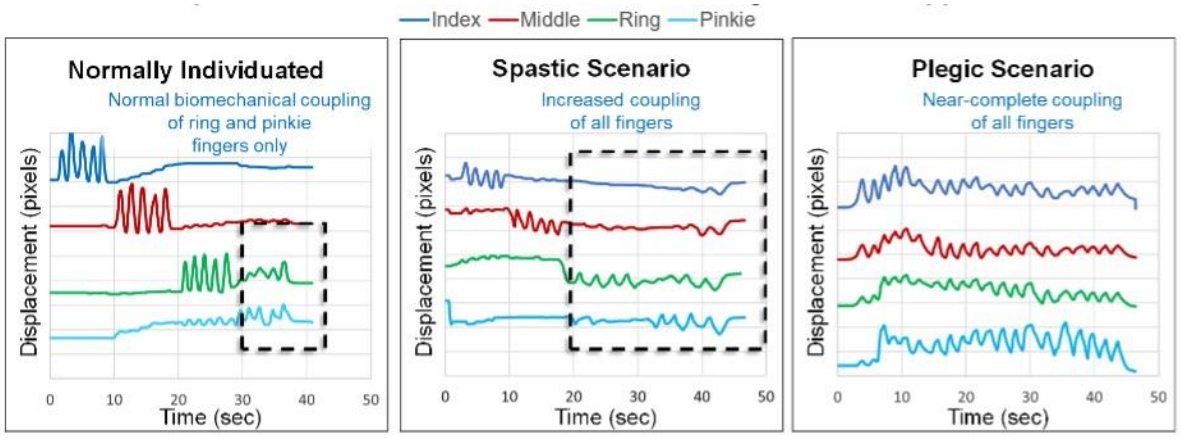
**Program #/Poster #:** PSTR020.25/R4

**Topic:** C.09.Stroke

**Title:** Quantifying fine motor impairments post-stroke at the bedside using a touch-screen app

**Authors: *M. E. PAULING**[1], E. CHOE[2], K. LEE[3], R. BRAUN[1];
[1]Neurol., Univ. of Maryland, Baltimore, MD; [2]Univ. of Maryland Col. of Information Studies, College Park, MD; [3]Univ. of Maryland, Human-Computer Interaction lab, College Park, MD

**Abstract:** Stroke is a leading cause of motor disability worldwide. Even in mild stroke it is often difficult for patients to regain their prior level of function due to persistent impairments in fine hand movement. This is especially true for skilled hand tasks such as computer and smartphone use. Deviations from normal finger individuation are common post-stroke and have been quantified using the Finger Individuation Index (FI Index). The index ranges from zero to one, where the FI index approaches zero for a hand with preserved independent finger movement, and approaches 1 for a hand with no independent finger movement. Here we present a prototype touch-screen app developed by our Brain Rehab and Recovery Lab in collaboration with the Human Computer Interaction Lab that uses the FI Index to quantify fine motor impairments post-stroke. We demonstrate that kinematic measures obtained at bedside using this app can quantify common patterns of post-stroke hand impairment. Feasibility data for two types of severe hand impairment are presented in Figure X, showing that that the app is usable by patients across a range of hand impairment severities. This work contributes to a growing body of evidence for the use of tablet-based tasks in stroke rehabilitation. It also offers a means to make detailed kinematic analysis accessible beyond the walls of the research lab by deploying affordable, portable technologies that can be used at the bedside or in the community, and are easy to setup by any clinician or caregiver familiar with basic smartphone technology.




**Disclosures:** **M.E. Pauling:** None. **E. Choe:** None. **K. Lee:** None. **R. Braun:** None.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.26/R5

**Topic:** C.09.Stroke

**Support:** PACEN Grant HC19C0028
NRF Grant 2022R1A2C1007948

**Title:** The impact of carbon dioxide inhalation preconditioning on acute focal cerebral ischemia-reperfusion injury in a transient middle cerebral artery occlusion rat model.

**Authors: C. YOON**[1], J. JUNG[1], H. LEE[2], I. KWON[2], Y. KIM[1,2], J. HEO[1,2], *H. NAM[1,2];
[1]Dept. of Neurol., Yonsei Univ. Col. of Med., Seoul, Korea, Republic of; [2]Integrative Res. Ctr. for Cerebrovascular and Cardiovasc. Disease, Yonsei Col. of Med., Seoul, Korea, Republic of

**Abstract:** Ischemic stroke results in brain damage and impaired function due to disrupted blood flow. Given the limited clinical therapeutic options, there is a need for novel therapeutic approaches. Carbon dioxide ($CO_2$) is a potential vasodilator that regulates cerebral blood flow (CBF). Preconditioning is a potential strategy to reduce brain damage and deficits. Thus, this study aims to investigate the protective effects of $CO_2$ inhalation preconditioning in an acute focal ischemia-reperfusion rat model. Male Wistar rats (270-320g) inhaled 20% $CO_2$ mixed gas before a 90-min transient middle cerebral artery occlusion (tMCAO). $CO_2$ inhalation increased regional cerebral blood flow (rCBF) in the MCA territory (160.05 ± 9.44% vs. baseline, $p$<0.001). Without $CO_2$, tMCAO caused a 93.3% rCBF decrease, recovering by 82.61% after reperfusion. During tMCAO, rCBF decreased by 11.03 ± 3.04% after inhalation, rising to 113.74 ± 13.25% post-reperfusion ($p$<0.001). $CO_2$ inhalation raised $pCO_2$ (43.62 ± 6.54 mmHg vs. 33.15 ± 4.98 mmHg, $p$=0.001) and lowered $pO_2$ and pH (7.48 ± 0.4 vs. 7.43 ± 0.04, $p$=0.0039.). Neurological deficits were assessed at 24 h after tMCAO. $CO_2$-preconditioned tMCAO rats had lower mNSS compared to tMCAO rats (6±2.0 vs. 11±1.3, $p$<0.0001). In rotarod test, latencies in the sham and $CO_2$-preconditioned sham groups were both 300 sec, but $CO_2$-preconditioned tMCAO rats had significantly longer latency compared to tMCAO rats (99.5±53.5 sec vs. 27.5±8.7 sec, $p$=0.0006). $CO_2$ preconditioned tMCAO rats also had a smaller infarction size compared to tMCAO rats (17.4±4.1% vs. 30.8±3.7%, $p$<0.0001). Western blot analysis showed higher levels of ZO-1 (0.86 ± 0.77 vs. 0.49 ± 0.25, $p$=0.03), occludin proteins (0.97 ± 0.28 vs. 0.61 ± 0.2, $p$=0.0205), and PDGFRβ (1.11 ± 0.3 vs. 0.57± 0.28, $p$=0.0157) in the $CO_2$-preconditioned tMCAO group, indicating improved tight junction and BBB integrity. Immunofluorescence staining confirmed enhanced expression and localization of PDGFRβ, ZO-1, and occludin in the $CO_2$-preconditioned tMCAO group. Furthermore, $CO_2$ preconditioning reduced oxidative stress (8-OHdG), brain damage (MMP-9), and apoptotic cell death (cleaved caspase-3) in tMCAO group. In conclusion, our study demonstrates that $CO_2$ inhalation preconditioning effectively reduces brain damage, improves neurological outcomes, and modulated physiological parameters in tMCAO-induced brain injury. Moreover, $CO_2$ pretreatment significantly reduces oxidative stress and BBB disruption. These findings suggest $CO_2$ inhalation holds promise as a promising therapeutic approach for ischemic stroke, providing insights into key mechanisms involved.

**Disclosures: C. Yoon:** None. **J. Jung:** None. **H. Lee:** None. **I. Kwon:** None. **Y. Kim:** None. **J. Heo:** None. **H. Nam:** None.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.27/R6

**Topic:** C.09.Stroke

**Support:** NIH T32NS096050
NIH NINDS 1F31NS131020
NIH NICHD 1R01HD095975

**Title:** Probing Neural Mechanisms of Prism Adaptation Therapy Using Single and Paired-Pulse TMS

**Authors: *O. ALOBA, DPT**[1], J. M. HOPE, PH.D.[2], T. M. LEONE, BS[2], T. M. KESAR PT, PH.D.[2];
[1]Grad. Div. of Biol. and Biomed. Sci., [2]Sch. of Medicine, Dept. of Rehabil. Med., Emory Univ., Atlanta, GA

**Abstract: Background:** Prism adaptation therapy (PAT) is an effective treatment to reduce Spatial Neglect (SN) and improve function in people post-stroke. PAT may modulate output-associated cognitive processing deficits known as 'Aiming' SN. However, cortical plasticity mechanisms related to the behavioral effects of PAT are poorly understood. Non-invasive sensorimotor electrical stimulation (estim) upregulates corticomotor excitability and is used as a therapeutic adjunct to motor training. We predict that estim modulates input-associated cognitive processing known as 'Where' perceptual-attentional, or representational SN (Where SN). But, the feasibility, interactive effects, targeted neural substrates, and mechanisms of combining estim with PAT for the treatment of SN are not known. **Purpose**: To evaluate novel spatial-motor treatment strategies that combine PAT with estim and elucidate their effects on corticospinal and intracortical excitability. **Methods**: 10 young able-bodied individuals and 10 individuals with right hemisphere stroke (40-90 years, >3 months with SN) will participate in the study. We evaluated the effects of a single session of PAT training with estim vs. sham estim on visuospatial bias, corticomotor and intracortical excitability, and the associations of these neurophysiologic effects with the magnitude of PAT-induced sensorimotor adaptation. Before and after PAT, we evaluated SN (using behavioral pointing and computerized line bisection tasks) and corticomotor and intracortical excitability (using the amplitude of motor evoked potentials (MEPs) elicited in response to single and paired-pulse transcranial magnetic stimulation (TMS) delivered to M1. **Results**: Preliminary results on 8 able-bodied control participants (6Female, 2Male) provide pertinent information about the neural mechanisms of PAT in the unimpaired neurophysiological system. Our results show that PAT with estim induces larger increases in MEP amplitude (+0.39±0.54mV) versus PAT with sham estim (-0.49±1.23mV). We also observed a larger after-effect in proprioceptive pointing in PAT with estim (-2.64±2.11cm) and PAT with sham estim (-1.88±2.27cm). **Discussion:** Combining PAT and non-invasive estim can target neural substrates and SN mechanisms that neither therapeutic intervention can target alone, therefore improving both Aiming and Where cognitive processing deficits associated with SN. Our study will inform novel combinatorial motor spatial retraining approaches to enhance the rehabilitation of SN and motor function post-stroke.

**Disclosures: O. Aloba, DPT:** None. **J.M. Hope, Ph.D.:** None. **T.M. Leone, BS:** None. **T.M. Kesar PT, Ph.D.:** None.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.28/R7

**Topic:** C.09.Stroke

**Support:** Support: American Heart Association Predoctoral Fellowship (900190)

**Title:** Activity-dependent dendritic spine dynamics in peri-lesion and contra-lesion cortices

**Authors: *V. NEMCHEK**, C. J. HOANG, M. MCCREA, V. SATHEESH, D. SUNDARARAMAN, T. A. JONES;
Univ. of Texas, Austin, Austin, TX

**Abstract:** After a stroke, areas physically near the lesion core (i.e., peri-lesion areas) experience increases in plasticity triggered by the injury. Plasticity also depends on neural activity in critical windows post-stroke. For example, rehabilitative training with the forelimb impaired by motor cortical stroke leads to adaptive plastic changes in the peri-lesion cortex. However, the role of plasticity in the less-affected hemisphere in recovery from stroke remains unclear. Compensatory reliance of the less-affected limb leads to maladaptive plasticity in both hemispheres; as such, limiting use of the less-affected limb, including physically constraining it, is a common therapeutic technique. Yet, contra-lesion plasticity appears to aid in recovery under certain conditions such as larger lesion volume. This study aims to illuminate activity-dependent plastic dynamics across hemispheres of the brain to help decipher the neural underpinnings of both impaired forelimb rehabilitation and coordinated use of both forelimbs.

Unimanual and bimanual rehabilitative training paradigms are used to compare activity-dependent structural plasticity in peri-infarct cortex and homotopic contra-lesion cortex after photothrombotic sensorimotor cortical stroke in Thy1-GFP mice. Bilateral cranial window implantations allow the use of *in vivo* two-photon imaging to compare dendritic spine dynamics between hemispheres for individual mice. After photothrombotic motor cortical ischemic stroke, mice either trained unimanually, bimanually, or received no training (Controls). The single seed reaching task targets the use of one forelimb (Unimanual) and is also used to assess impaired limb function. The Bimanual task is also a skilled reaching task but differs in that both forelimbs must be used cooperatively to retrieve a food reward.

Simultaneous activity-dependent plastic changes in both hemispheres are anticipated for both rehabilitative training groups (Unimanual and Bimanual). Preliminary results indicate different patterns of dendritic spine plasticity not only in mice with different rehabilitative experience, but also between hemispheres of each individual mouse. Early behavioral results suggest that unimanual rehabilitative training leads to the greatest functional recovery of the impaired limb.

Interhemispheric patterns of dendritic spine changes indicate that greater degrees of change in one hemisphere relate to an inverse pattern in the opposite cortex.

**Disclosures: V. Nemchek:** None. **C.J. Hoang:** None. **M. McCrea:** None. **V. Satheesh:** None. **D. Sundararaman:** None. **T.A. Jones:** None.

**Poster**

**PSTR020. Stroke Recovery: Non-Pharmacological Approaches to Therapy I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR020.29/Web Only

**Topic:** C.09.Stroke

**Title:** Induced gamma oscillations facilitate functional synaptic plasticity acutely after stroke

**Authors:** C. WANG[1], ***M. BALBI**[2];
[1]Queensland Brain Inst., St Lucia, Brisbane, Australia; [2]Univ. of Queensland, Brisbane, Australia

**Abstract: Background:** Changes in oscillatory brain patterns have been observed in several neurological disorders, including stroke. Evoked neural oscillations in the gamma range have recently shown the ability to restore and maintain intrinsic homeostatic processes in the brain. However, the causal relationship between stimulation and restoration of function is not well understood. **Aim:** Here, we aimed to determine the mechanisms behind the observed neuroprotective effects following optogenetic stimulation at 40 Hz by characterising electrophysiology and genomic profiling of inhibitory neurons. **Method:** We used optogenetic stimulation together with laser speckle imaging, electrophysiology, and RNA sequencing in a photothrombotic stroke model in awake mice, to investigate the effects of gamma-waves modulation in the acute phase after stroke. **Result/Conclusion:** We show that optogenetic stimulation at 40 Hz drives activation of inhibitory neurons specifically. We found that following stroke induction in the motor area (M1), 40 Hz stimulation enhances interregional communication between M1 and the parietal association area (PTA), and interestingly this is still present 24 hours after stimulation. Cross-correlogram analysis indicates that optogenetic stimulation of inhibitory neurons in the gamma range leads to an increase in functional synaptic plasticity observed 24 hours after stroke induction. Our results suggest that modulation of cortical oscillatory dynamics may serve as a target for neuroprotection after stroke by modulating synaptic connections.

**Disclosures: M. Balbi:** None.

**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.01/R8

**Topic:** C.10. Brain Injury and Trauma

**Support:** NSF Grant 2138719
UTSA Start-UP

**Title:** Using Computer Vision-based Segmentation Approaches for Automatic Detection of Astrocyte Reactivity Following Traumatic Brain Injury

**Authors:** M. VESANEN[1], A. BAGHERIAN[1], J. SILVA[2], A. KOSUB[1], A. PATTERSON[1], K. DESAI[2], ***M. HAJIAGHAMEMAR**[3];
[1]Biomed. Engin. and Chem. Engin., [2]Dept. of Computer Sci., [3]Univ. of Texas at San Antonio, San Antonio, TX

**Abstract:** Traumatic brain injury (TBI) is the leading cause of cognitive and behavioral deficits worldwide with millions of occurrences annually. Astrocyte reactivity, which is assessed by GFAP immunohistochemistry, is widely used in TBI studies for evaluating the injury severity and mechanism and effectiveness of therapeutic interventions. There are currently two common methods for quantifying astrocyte reactivity: manual labeling and intensity thresholding. However, manual labeling is tedious and time-consuming, and intensity thresholding is very sensitive to staining and imaging process, requiring many manual adjustments. There is a strong need for automatic and accurate detection of TBI-induced astrocyte reactivity. In this study, we explored several state-of-the-art Computer Vision-based segmentation approaches for identifying astrocyte pixels in the 113 images of size 512x640 curated from 2 microscope images of TBI-induced ferret brain slices with GFAP staining. All the images were normalized to have same overall average intensity on the pixels containing tissues prior to their use by the segmentation models. One of the major drawbacks in the use of modern deep learning approaches for astrocyte reactivity detection is the need for a large dataset. To overcome this, we used two different data augmentation techniques, namely ColorJitter and horizonal flipping, to increase the size of the dataset by three times. We compared six segmentation approaches, namely FPN, Unet, Unet++, MAnet, Linknet, and PSPnet, where the backbone encoder architecture was set to be Resnet101. We ran each of the six models on the original dataset as well as the augmented dataset to evaluate its performance effect. All the models were taken from the implementations available in the PyTorch libraries. We used 5-fold cross validation, where each fold ran for 20 epochs of going through the images one at a time. To compare the approaches, we used different metrics - accuracy, F1, Sensitivity, Specificity, and IOU. The experimental results indicated that Unet++ was the best method with the values for the above metrics being 99.42%, 0.8415, 0.8457, 0.9974, and 0.7528, respectively. It was also observed that the applied dataset augmentation approach helped improve the performance for all models. Specifically, for Unet++, the metric values obtained were 99.55%, 0.8918, 0.8904, 0.9979, and 0.8167 respectively. These results indicated that using neural networks and applying data augmentation techniques can significantly help advance the detection and quantification of astrocyte reactivity following TBI and pathology evaluation in general. Funding from UTSA and partially by NSF-2138719.

**Disclosures:** **M. Vesanen:** None. **A. Bagherian:** None. **J. Silva:** None. **A. Kosub:** None. **A. Patterson:** None. **K. Desai:** None. **M. Hajiaghamemar:** None.

**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.02/S1

**Topic:** C.10. Brain Injury and Trauma

**Support:** CNRM-70-8956
USU- PAT-74-3439
CDMRP W81XWH-13-2-0018

**Title:** Blast TBI presents with persistent inflammatory markers in the cerebral cortex associated with neuronal targeted autoantibody mediated complement pathology.

**Authors: *N. R. BREEHL**[1], S. C. SCHWERIN[4], M. CHATTERJEE[2], D. PRIEMER[3], D. PERL[3], S. JULIANO[1];
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**Abstract:** Traumatic Brain Injury (TBI) resulting from head impacts, blast exposure, or whiplash-like phenomena, are a major cause of death and disability, especially in the military. We developed an injury model for TBI in the ferret, designed to be similar to that encountered from combat exposure. To enhance translatability, we also studied posthumous samples from military personnel exposed to blast TBI. Blast TBI leads to chronic and diffuse inflammatory markers, with increased GFAP (astrocytes) and IBA1 (microglia) immunoreactivity, lasting at least 6-months post injury in the ferret and many years in people. Since increased astrogliosis occurs at interfaces of tissue with differing density, we measured the complexity of astrocytes at several of these sites in the ferret, and at neocortical blood vessels in the human. While ferret astrocytes were significantly more complex after injury, human astrocyte morphology altered significantly to appear beaded/fragmented, and often lost fine branches. As astrocytes are highly involved in central nervous system homeostasis, we measured changes in expression of several involved proteins. Aquaporin-4 (AQP4), a water channel protein, is expressed in the endfeet of astrocytes making up the glial limitans of the blood brain barrier and is crucial to the glymphatic system. Connexin-43 (conn43), a gap junction protein, allows astrocytes to perform spatial buffering and form glial syncytia. Ferrets show increased AQP4 after injury with significant GFAP colocalization at neocortical interfaces, indicating altered AQP4 localization; AQP4+ astrocytes do not exist as a distinct population in ferrets. Control human tissue, however, shows largely equal sub-populations of AQP4+ and GFAP+ astrocytes, while injured tissue demonstrates a shift towards GFAP+, with abnormal morphology, or reactivity for both GFAP+/AQP4+. Human tissue stained for conn43 co-labels with AQP4+ astrocytes while GFAP+ astrocytes remain a separate population, indicating AQP4+ astrocytes act as homeostatic regulators. Occasionally, an astrocyte appears conn43+ and GFAP+ but shows phenotypically normal morphology after TBI, suggesting AQP4+ astrocytes shift from a homeostatic regulator toward a reactive state. Phosphorylated conn43, however, contributes to inflammation and layer

1 astrocytes in human samples increase expression of p-conn43 after injury. Finally, to determine if blast TBI may induce autoimmunity, we observed IgG reactivity after injury, predominantly labeling pyramidal neurons, as well as interlaminar astrocytes. These same cells also co-label with complement C3, indicating autoantibody mediated complement targeting.

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**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.03/S2

**Topic:** C.10. Brain Injury and Trauma

**Title:** Astrocytic changes after closed-head, rotational acceleration TBI in swine

**Authors: *D. J. HAN**[1,2], K. D. BROWNE[2,1], N. A. FEDORCZAK[2,1], M. R. GROVOLA[2,1], E. KRIZMAN[2,1], D. PETROV[2], D. K. CULLEN[2,1,3], J. O'DONNELL[2,1];
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**Abstract:** Recapitulating the injury mechanisms and manifestations observed in humans is necessary to maximize translational relevance in preclinical studies of traumatic brain injury (TBI). For mild TBI, that means closed-head rotational acceleration to load injurious forces proportional to brain mass, resulting in less than 30 min of unconsciousness and no focal lesions to match clinical diagnostic criterea. A relatively large gyrencephalic brain with high white matter content similar to humans is necessary to allow for scaling up rotational acceleration to compensate for lower brain mass and achieve the injurious forces generated in human TBI. Acceleration would need to be scaled up 8000x in the small, licencephalic, low white matter brains of rodents, which—despite attempts made with the misinformation-laden CHIMERA "model"—cannot be achieved. Currently, the only model in use that can recreate these TBI mechanisms and manifestations utilizes head rotational acceleration in swine. Our group has previously conducted in-depth histological analyses of microglia over time following mild TBI in this swine model. However, the only analysis performed for astrocytes was cursory scoring of "reactivity" based on GFAP staining. Astrocytic responses to injury cannot be summarized by such analysis. Therefore, we sought to delve deeper by testing for changes in the key astrocytic proteins GLT-1 (a glutamate transporter responsible for preventing excitotoxicity at the synapse) and AQP4 (a water channel that is involved in maintaining optimal intracranial pressure). Following injury, GLT-1 levels decrease, disrupting cerebral metabolism and creating an excitotoxic environment; and AQP4 increases, which has been implicated in contributing to edema. These astrocytic proteins perform essential functions for brain health, and after injury their disruption has major implications for secondary injury. Studying these cellular changes in a

clinically relevant large animal model of TBI provides significant insight into mechanisms of secondary injury and elucidates potential therapeutic targets.

**Disclosures: D.J. Han:** None. **K.D. Browne:** None. **N.A. Fedorczak:** None. **M.R. Grovola:** None. **E. Krizman:** None. **D. Petrov:** None. **D.K. Cullen:** None. **J. O'Donnell:** None.

**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.04/S3

**Topic:** C.10. Brain Injury and Trauma

**Support:** K99 NS125039
F32 NS116205
R01-NS117757

**Title:** Linking neuropathology and immune system dysregulation following a closed-head diffuse traumatic brain injury in female swine

**Authors: *K. L. WOFFORD**[1,3], K. D. BROWNE[1,3], D. CULLEN[1,3,2];
[2]Bioengineering, [1]Univ. of Pennsylvania, Philadelphia, PA; [3]Ctr. for Neurotrauma, Neurodegeneration and Restoration, Corporal Michael J. Crescenz VA Med. Ctr., Philadelphia, PA

**Abstract:** Closed-head rotational injury is the most common form of traumatic brain injury (TBI) and increases the risk for cognitive impairments, neurodegeneration, and substance abuse. Additionally, reduced immune functionality is common after TBI, causing an increased vulnerability to infection, which is associated with poorer neurological outcome. However, the relationships between TBI, neuropathological endophenotypes, and immunological dysregulation have never been studied in a clinically relevant model of closed-head rotational injury. To investigate these relationships, we employed a translational preclinical model of diffuse closed-head rotational TBI to characterize the extent and distribution of neuropathology and the correlating changes to the immune system over time. We hypothesized that acute damage to specific regions of the brain would temporally correlate with disruptions to peripheral immune cell composition and function. To test this, female Yucatan minipigs experienced a sham (n=3) or a moderate-to-severe TBI (n=7; 105-115 rad/s). Sham animals and a subset of TBI animals (n=4) survived for 14-days post injury, while the remaining animals survived 3-days post injury. Peripheral whole blood was collected prior to injury and at multiple timepoints post injury for each animal. Extracted brain tissue was stained with hematoxylin and eosin to assess gross pathological changes; fibrinogen to ascertain BBB breakdown; and Iba1 to identify microglia density and morphology. Peripheral blood mononuclear cells (PBMCs) were extracted from whole blood with a Ficoll density gradient and were phenotypically characterized with flow cytometry. We identified an increase in BBB breakdown 3-days post TBI, with evidence of

microthrombi, larger vessel occlusion, and serum extravasation into the brain parenchyma. Most of the observed BBB pathology was localized to white matter regions of the brain, primarily paraventricular and ventral regions. Furthermore, we observed changes to microglial morphology 3-days post TBI, with evidence of microglial cells aggregating in white matter regions of the brain. These cellular aggregates were not observed following a sham procedure or 14-days post TBI. In tandem, the number of circulating PBMCs increased 3-days post injury (p&lt0.001) while PBMC composition was changed 6 hours after injury with an increase in the fraction of circulating myeloid cells (p&lt0.01). Together, these data suggest that there are co-occurring changes in the brain and periphery 3-days post TBI. Ongoing, analyses seek to characterize the extent of neuropathological burden in regions known to modulate peripheral immune function.

**Disclosures: K.L. Wofford:** None. **K.D. Browne:** None. **D. Cullen:** None.

**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.05/S4

**Topic:** C.10. Brain Injury and Trauma

**Support:** US Army Combat Casualty Care Research Program
CO210048_WRAIR_AHS, and H_001_2018_WRAIR_JDP

**Title:** Mitochondrial Bioenergetic Disregulation in a Swine Model of Traumatic Brain Injury and Polytrauma

**Authors: J. D. PANDYA**, H. R. MODI, S. MUSYAJU, Z. BAILEY, M. HANSON, D. SHEAR, A. H. SCULTETUS;
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**Abstract:** Traumatic brain injury (TBI) frequently occurs in combination with polytrauma. Polytrauma injuries to vital organs like lungs, liver, kidneys and heart resulted in devastating compounded pathophysiological effects. After TBI or polytrauma, a cascade of events leads to an array of secondary injury processes and cell death responses. Several TBI studies have ascertained that mitochondrial dysfunction is an acute first-indicator of cellular damage, and plays a critical role in long-term disease progression. Extending our understanding of post-injury mechanisms following TBI, we collected multi-organ reference data in a swine model. The swine model has recently come to the forefront as their large brain mass and gyrencephalic architecture are key features in replicating the biomechanics and pathophysiological progression of closed-head TBI and polytrauma pathophysiology in humans. At 4hr post-craniotomy, mitochondria from Yorkshire swine (30-35g) vital organs were isolated for bioenergetics and $Ca^{2+}$ buffering capacity assessment. Stored mitochondria were assessed for membrane integrity, oxidative stress, and apoptotic markers using immunoblotting. Compared to other organs, brain and heart displayed the maximum bioenergetics and $Ca^{2+}$ buffering capacity.Likewise, both

organs showed higher expression of membrane proteins cytochrome C and VDAC. Antioxidants superoxide dismutase, thioredoxin and peroxiredoxin revealed organ-specific differential expressions. Interestingly, catalase expression was highest in the liver. We observed muti-organ and brain region-specific differences in mitochondrial parameters in control swine. The vital organs are equipped with unique profiles to combat pathological insults. Multi-organs reference values may provide valuable insights into developing mitochondria-targeted therapeutic interventions for TBI and polytrauma.
Disclaimer: Material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author(s), and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense. Research was conducted under an IACUC-approved animal use protocol in an AAALAC International - accredited facility with a Public Health Services Animal Welfare Assurance and in compliance with the Animal Welfare Act and other federal statutes and regulations relating to laboratory animals.

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**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.06/S5

**Topic:** C.10. Brain Injury and Trauma

**Support:** NIH Grant R21NS117867
NIH Grant R01 NS091218

**Title:** Peroxisomal ether phospholipid synthesis is dysregulated in the brain after TBI

**Authors: *C. SARKAR**[1], N. U. HEGDEKAR[1], S. BUSTOS[1], Y. MOREL[2], Y. JI[2], A. MEHRABANI-TABARI[1], S. THAPA[1], O. PETTYJOHN-ROBIN[1], J. JONES[2], M. M. LIPINSKI[1];
[1]Univ. of Maryland, Baltimore, MD; [2]Univ. of Maryland Sch. of Pharm., Baltimore, MD

**Abstract:** Ether phospholipids are glycerophospholipids that contain an ether bond at the sn-1 position of the glycerol backbone. They are major components of membrane lipid raft, play an important role in membrane trafficking and cell signaling, and provide protection to the membrane structure against oxidative stress. They constitute almost 20% of brain lipids. Their deficiency has been implicated in different neurodegenerative diseases. However, how ether phospholipids are regulated after traumatic brain injury (TBI), a devastating neurodegenerative disease caused by the impact of external forces to the brain due to fall, accident or assault is not clearly known. In this study, we determined the levels of ether phospholipids in the cortices of sham and TBI mice using liquid chromatography tandem mass spectrometry (LC-MS/MS) based

lipidomic analysis. Our data showed a significant decrease in ether phospholipid abundance in the injured mouse cortices following controlled cortical impact (CCI) induced TBI as compared to the sham mice. This is at least in part due to the dysregulation of ether phospholipid synthesis in the brain following TBI. Ether phospholipid synthesis begins within the peroxisome generating ether-phospholipid precursors that are converted into fully formed ether phospholipids in the endoplasmic reticulum (ER). We detected a marked decrease in the levels of peroxisomal ether phospholipid synthesizing enzymes - fatty acyl-CoA reductase 1 (FAR1) and glyceronephosphate O-acyltransferase (GNPAT) in the cortices of TBI mice as compared to that of sham mice. This suggests that peroxisomal ether phospholipid synthesis is impaired in the mouse brain following TBI. To restore ether phospholipids level in the injured brain, we fed TBI mice with an ether phospholipid precursor - 1-O-octadecylglycerol (OAG) to bypass peroxisomal ether phospholipid synthesizing steps. The levels of several ether phospholipids in the injured cortices of mice fed with OAG were partially restored as compared to the untreated TBI mice. We detected a decrease in inflammatory markers in the injured cortices of mice fed with OAG as compared to that of untreated TBI mice. We also observed functional improvement in these mice as compared to the untreated injured mice. Taken together, our data demonstrate that ether phospholipid is dysregulated in the cortices after TBI at least in part due to peroxisomal impairment and its restoration in the injured brain by its precursor treatment is beneficial in restricting functional deficits in TBI mice.

**Disclosures:** **C. Sarkar:** None. **N.U. Hegdekar:** None. **S. Bustos:** None. **Y. Morel:** None. **Y. Ji:** None. **A. Mehrabani-Tabari:** None. **S. Thapa:** None. **O. Pettyjohn-Robin:** None. **J. Jones:** None. **M.M. Lipinski:** None.

**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.07/S7

**Topic:** C.10. Brain Injury and Trauma

**Support:** RO1 NS115876

**Title:** The role of LC3-associated phagocytosis in traumatic brain injury mice model

**Authors: *S. THAPA**, A. M. TABARI, N. HEGDEKAR, C. SARKAR, M. M. LIPINSKI; STAR, Univ. of Maryland, Baltimore, Baltimore, MD

**Abstract:** Traumatic Brain Injury (TBI) is a global health concern that can cause neurological deficit, neurodegeneration, and death. TBI leads to secondary inflammatory responses in the nervous system due to neuronal cell death and release of endogenous Damage Associated Molecular Patterns (DAMPs). We recently demonstrated that macroautophagy (autophagy), a lysosome-dependent cellular catabolic pathway, is inhibited in activated microglia and infiltrating monocytes after TBI in a mouse model, and that this contributes to inflammation.

Both inhibition of autophagy and inflammation were exacerbated in mice with microglia/macrophage specific knock out of the essential autophagy mediator *Becn1*. *Becn1* regulates both canonical autophagy and a non-canonical pathway termed LC3-associated phagocytosis (LAP), each of which has been implicated in regulation of inflammation. While LAP shares some components, such as Beclin1 and LC3, with autophagy, it uniquely requires presence of the type III PI3 kinase component, Rubicon and the phagocytic mediator NOX2. LAP is involved in phagocytosis of extracellular cargoes such as dead/dying cells and DAMPs, which are abundant after TBI. Therefore, we hypothesized that LAP inhibits neuroinflammation and promotes recovery after TBI. Our data suggest that LAP is involved in the clearance of DAMPs and myelin debris released after injury. TBI induced accumulation of LAPosomes (LC3+NOX2+ phagosomes) in activated macrophages and microglia. TBI in *Becn1* KO mice resulted in DAMP accumulation in the injured cortex tissue and reduced phagocytic capacity of microglia. Furthermore, TBI led to impaired neurological functional outcomes in *Becn1* KO mice and altered pro-inflammatory responses in *Rubcn* KO mice. In addition to dead cells and DAMPs, TBI leads to generation of abundant myelin debris, and we hypothesized that LAP may be involved in its removal. Consistently, *in vitro* assays using *Rubcn* deficient bone marrow-derived macrophages (BMDMs) demonstrated that LAP deficiency leads to increased accumulation of myelin debris and lipid droplets within these cells. Together, these findings indicate that LAP participates in phagocytosis and degradation of debris and lipids in macrophages/microglia, thereby contributing to resolve neuroinflammation and promoting recovery after TBI.

**Disclosures: S. Thapa:** None. **A.M. Tabari:** None. **N. Hegdekar:** None. **C. Sarkar:** None. **M.M. Lipinski:** None.

**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.08/S8

**Topic:** C.10. Brain Injury and Trauma

**Support:** Research Eureka Accelerator Program (REAP) Award issued from the Edward Via College of Osteopathic Medicine (VCOM) and Virginia Tech Institute for Critical Technology and Applied Science (ICTAS) partnership

**Title:** Emergence of chronic depression-like behavior and changes in N-methyl-D-aspartate receptor expression following closed-head impact traumatic brain injury

**Authors: *C.-E. T. TALTY**[1], S. F. MURPHY[2], P. J. VANDEVORD[2,3];
[1]Grad. Program in Translational Biology, Med. and Hlth., [2]Biomed. Engin. and Mechanics, Virginia Tech., Blacksburg, VA; [3]Veterans Affairs Med. Ctr., Salem, VA

**Abstract:** Concussions represent a significant public health burden in the United States and around the globe due to the somatic, emotional and cognitive symptoms that plague individuals following this type of injury. Longitudinal studies suggest that up to half of concussion patients suffer from persistent adverse symptoms that may last months or even years after the initial injury. Emotional symptoms and mood disorders are especially concerning as elevated rates of depression and suicide are observed in those with persistent post-injury symptoms. Long-term alterations in glutamatergic signaling proteins have been identified as a possible link between traumatic brain injury (TBI) and depression due to independent observations of glutamate transporter downregulation and N-methyl-D-aspartate receptor (NMDAR) subunit expression changes in both TBI and major depressive disorder (MDD) patients. We assessed the development of depression-like behavior at four, eight- and twelve-weeks post-injury in a preclinical model of concussion. A closed-head controlled cortical impact (cCCI) model was used in adult male rats. The splash test, three-chamber sociability and social novelty tests were used to measure deficits in self-care/apathy and social preferences, respectively. Decreased grooming behaviors, indicative of self-care deficits, were observed by eight weeks in injured animals and maintained through twelve weeks. Loss of social novelty preference emerged by four weeks, while sociability deficits were evident by eight weeks in injured animals, with deficits in both behaviors persisting through twelve weeks. Brain tissue was collected at twelve weeks post-injury and Western blot was used to assess expressional changes in NMDAR subunits GluN1, GluN2A and GluN2B, as well as astrocytic glutamate transporters GLT-1 and GLAST, in the frontal cortex and hippocampus. Significant increases in both GluN1 and GluN2A were observed in the frontal cortex of injured animals, while the hippocampus exhibited no significant changes in expression of proteins of interest at this timepoint. Together these findings suggest that chronic depression-like behavior resulted from a single closed-head impact and, in some cases, did not emerge until several weeks following injury. Furthermore, injured animals demonstrated increased expression of NMDAR subunits in the frontal cortex which may have been in response to decreased extracellular glutamate levels at this timepoint. Future work should evaluate longitudinal alterations in extracellular glutamate concentration post-injury in addition to investigating sex as a biological variable in this context.

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**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.09/S9

**Topic:** C.10. Brain Injury and Trauma

**Support:** DOD W81XWH-20-1-0635
WBI TR192003

**Title:** Leveraging multidimensional whole brain imaging and spatial transcriptomics to investigate the pathophysiology of murine traumatic brain injury

**Authors: *M. ANWER**[1,2], A. ZHANG[3], B. BRISTOW[3], J. LEDUE[1], Z. WANG[1], S. WANG[1], L. KRAUS[3], W. H. CHENG[2,1], K. MCINNES[4], J. FAN[2,1], H. CHEUNG[2,1], C. BARRON[1], P. A. CRIPTON[4,1], T. H. MURPHY[1], F. ROSSI[4], M. S. CEMBROWSKI[3,1], C. L. WELLINGTON[2,1]; [1]Djavad Mowafaghian Ctr. for Brain Hlth., [2]Pathology and Lab. Med., [3]Cell. and Physiological Sci., [4]Sch. of Biomed. Engin., Univ. of British Columbia, Vancouver, BC, Canada

**Abstract:** Traumatic Brain Injury (TBI) is extraordinarily heterogeneous in clinical presentation and results in diffuse white matter injury, inflammation, vascular damage, and neuronal dysfunction. The lack of reliable temporal molecular signatures and translational biomarkers can limit relevance of animal models to human TBI. The Closed Head Impact Model of Engineered Rotational Acceleration (CHIMERA) is a non-surgical model of impact-acceleration injury that mimics the biomechanics and pathophysiology of human TBI. We investigated histological and molecular changes in the diffusely injured murine brain after CHIMERA TBI using light sheet microscopy (LSM) and spatial transcriptomics (10X Visium). c-FosTRAP2 mice, which stably express neuronal c-Fos upon tamoxifen injection, were randomly assigned to a TBI or sham group. Animals were assessed for acute neurological deficits and blood was collected at 6 hours post-TBI for injury-related biomarker assessment. SHIELD-fixed passively cleared whole brains were imaged using LSM equipped with a specialized whole-brain imaging chamber. For Visium, immunohistochemical readouts were first established to map gene expression profiles to glia and neurons. Sections then underwent cDNA synthesis and library construction, followed by Illumina NextSeq500 sequencing. Reads were quantified via SpaceRanger and Seurat R package. We found prolonged loss of righting reflex and neurological severity score as well as elevated plasma neurofilament light chain and glial fibrillary acidic protein levels in TBI group compared to sham at 6h post-TBI. We developed a pipeline for image stitching, rendering, cell segmentation and registration with Allen Mouse Brain Atlas using ARIVIS and BrainQuant3D software and identified unique 3D spatial patterns of c-Fos+ cell density in the TBI group indicating distinct alterations in neuronal activity pattern. Using Visium, we obtained transcriptomic information for 55-µm diameter circular regions tiling an entire section of brain (4992 sequenced regions/section) with strong replicate reproducibility within groups. Within an initial dataset of >1B reads, we identified differential gene expression and unique clusters in TBI compared to sham groups across two distinct atlas regions (bregma -2.0 and -3.0 mm) containing isocortex, hippocampus, thalamus and amygdala. Importantly, we observed decreased interneuron labelling in TBI compared to sham mice - consistent with interneuron dysregulation and/or death following TBI. This study established proof-of-concept data supporting the hypothesis that TBI results in brain-wide changes in gene expression and neuronal activity.

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**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.10/S10

**Topic:** C.10. Brain Injury and Trauma

**Support:** NIH Grant 1R01NS121246-01

**Title:** Neurovascular and Behavioral Deficits after Traumatic Brain Injury

**Authors: *A. SINGH**[1], S. GONG[2], A. VU[2], A. OBENAUS[1];
[1]Pediatrics, Univ. of California, Irvine, Irvine, CA; [2]Univ. of California Irvine, Irvine, CA

**Abstract:** Traumatic brain injury (TBI) is a silent epidemic, and many survivors face debilitating long-term consequences ranging from depression and dementia to increased suicidal tendency. Adverse effects on neurovascular physiology and rodent behavior are apparent early after injury, however there is a gap in our understanding of long-term deficits arising after TBI. Previously, we observed vascular recovery in the cortex around TBI using in vivo 2photon-microscopy in rodents (Lin et al 2022). In our study we longitudinally investigated the recovery of neurovascular structures and physiology in male and female mice for up to 60 days post injury (dpi). Adult C57/BL6 male and female mice underwent a moderate controlled cortical impact injury (1mm depth). At baseline, 3-, 7-, 14-, 30-, and 60-dpi MRI (9.4T) assessments included: T2-weighted, T1-pre/post and contrast-enhanced perfusion (gadolinium via tail vein, 0.1µmol/g). Foot-fault, open-field, and social behaviors before each MRI session were acquired. Cerebral blood flow (CBF) was reduced in TBI animals vs. shams at 3dpi that extended from the cortical impact site to adjacent and even to distant brain regions including somatosensory, piriform, hippocampus, caudate, and hypothalamus. CBF transiently recovered at 7-30 dpi but then decreased by 60dpi that mirrored a loss of vasculature at the impact site. Behaviorally, TBI animals exhibited decreased cage-mate preference at 60dpi vs. shams. Our temporal neurovascular findings demonstrate CBF recovery followed by latent decrements that coincide with vascular and behavioral impairments. Thus, late changes in perfusion may underlie the emergence of psycho-social decrements observed in TBI subjects later in life. These data can guide translational TBI research into future therapeutics.

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**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.11/T1

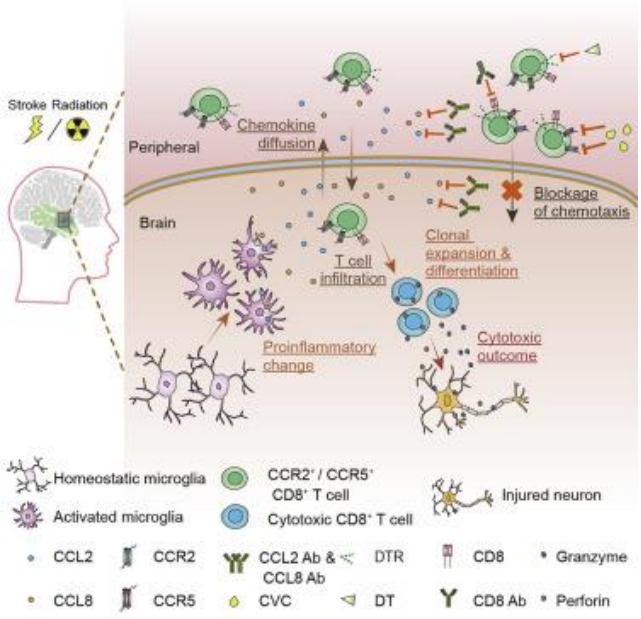
**Topic:** C.10. Brain Injury and Trauma

**Support:** NSFC 81925031
NSFC 81820108026
Guangzhou Science and Technology 202007030001 Program key projects
NSFC 82103775

**Title:** Microglia drive radiation-induced brain injury by chemotactic recruitment of $CD8^+$ T lymphocyte

**Authors: *Z. SHI**[1], X. HU[1], W.-J. LIN[2], S. CHEN[1], S. LI[1], Y. TANG[1];
[1]Dept. of Neurol., [2]Med. research center, Sun Yat-Sen memorial hospital, Guangzhou, China

**Abstract:** Interactions between the adaptive immune system and the central nervous system (CNS) have gained increasing attention for their critical roles in many neurological diseases, but the underlying mechanisms remain underinvestigated. Radiation-induced brain injury (RIBI) is a chronic neurological disease and the most common complication of cranial radiotherapy in patients with head and neck tumors. Here, we applied single-cell RNA and TCR (T cell receptor) sequencing to analyze lesioned brain tissues surgically removed from patients with RIBI. We found infiltration and clonal expansion of $CD8^+$ T lymphocytes in the lesioned brains. Using a gamma ray-induced RIBI mouse model, we demonstrated that systemic ablation of $CD8^+$ T cells effectively ameliorated brain lesions. Furthermore, we identified CCL2- and CCL8-expressing microglia as the key mediator for the infiltration of $CCR2^+$ $CD8^+$ and $CCR5^+$ $CD8^+$ T cells, whereby genetic or pharmacological interruption of the chemotactic axis significantly reduced parenchymal $CD8^+$ T cells and alleviated brain lesion in the RIBI mice. We further confirmed that the same chemotactic interaction mediating $CD8^+$ T cell infiltration is involved in the development of cerebral infarction in a mouse model of ischemic injury. Together, our findings reveal a previously unidentified chemotactic recruitment of $CD8^+$ T cells into brain parenchyma by microglia, providing a new therapeutic strategy for RIBI and ischemic stroke.

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**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.12/T2

**Topic:** C.10. Brain Injury and Trauma

**Support:** R01 NS115876

**Title:** Lysosomal accumulation of lipids leads to autophagy inhibition in microglia and macrophages and contributes to inflammation after traumatic brain injury

**Authors: *A. MEHRABANI-TABARI**[1], N. HEGDEKAR[1], Y. MOREL[2], L. MULLER[2], C. SARKAR[1], M. KANE[2], J. JONES[2], M. LIPINSKI[1];
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**Abstract:** Traumatic brain injury (TBI) induces excessive and prolonged inflammation which is a contributing factor to poor prognosis in TBI patients. Resident microglia and infiltrating monocytes are major mediators of the pro-inflammatory response. We recently showed that autophagy, a lysosome-dependent intracellular catabolic pathway, is inhibited in microglia and infiltrating monocytes after TBI, and that this contributes to their exacerbated pro-inflammatory phenotype. However, the mechanism of autophagy inhibition needs to be addressed. Brain tissue is very rich in lipid, particularly cholesterol, and our data show a significant change in the lipid composition of perilesional TBI tissue confirmed by DESI-MSI lipid imaging, and LC-MS/MS lipidomic analyses. This study tests the hypothesis that phagocytosis of lipid debris, especially cholesterol-rich fragmented myelin, in the microenvironment of TBI lesion by monocytes inhibits lysosomal degradation in these cells, leading to autophagy dysfunction. Our lipidomic analyses revealed pronounced accumulation of lipids in cell-sorted monocytes and in lysosomes purified from the peri lesion area. This included myelin components (cholesterol esters, sphingomyelin, and ceramides) and neutral lipids (triglycerides) consistent with lipotoxicity. We also observed neutral lipid accumulation and lipid droplet formation in activated monocytes after TBI, shown by both immunofluorescent staining and flow cytometry, reaffirming that monocytes uptake lipid rich debris. Autophagy markers, LC3-II and P62/SQSTM1, accumulated in the same phagocytes that showed lipid accumulating phenotype, suggesting lipid accumulation and autophagy inhibition are connected. We next tested the causation between lipid phagocytosis and autophagy inhibition and the potential mechanism of the effect *in vitro*. We treated murine primary bone marrow derived macrophages (BMDM) with purified myelin and observed phagocytosis-dependent accumulation of intracellular myelin and formation of lipid droplets. Myelin phagocytosis led to autophagy inhibition, as confirmed via western blotting, immunofluorescence, and flow cytometry. Moreover, by two functional activity assays, we detected significant decrease in the activity of lysosomal enzymes, Cathepsin-D and N-acetyl-glucosaminidase (NAG), confirming lysosomal dysfunction. In conclusion, our data indicate that auto-lysosomal degradation is inhibited in monocytes due to excessive lipid phagocytosis after TBI, and support the need for further investigation of the link between lipid metabolism, autophagy and inflammation as a potential therapeutic target for TBI.

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**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.13/T3

**Topic:** C.10. Brain Injury and Trauma

**Support:** Partially supported by PAPIIT IN228223

**Title:** Fractal analysis of morphological changes in microglia during day and night in the motor cortex in a rat model of traumatic brain injury.

**Authors: *K. DIAZ DUARTE**[1], R. MARTINEZ-TAPIA[1], F. ESTRADA-ROJO[1], T. LOPEZ-ACEVES[3], V. RODRÍGUEZ-MATA[2], E. PULIDO-CAMARILLO[2], A. PEREZ-TORRES[2], L. SANCHEZ-MARTINEZ[1], M. DE LAS CASAS CERVANTES[1], F. ESPINOSA-BECERRA[1], L. NAVARRO[1];
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**Abstract:** Traumatic brain injury (TBI) is defined as an alteration of brain function or other evidence of brain pathology caused by an external force. Microglia activation plays a key role in protecting and repairing the brain against the damage of a TBI. Microglia morphology may reflect their function and ability to respond to immunological stimuli depending on the hour of the day. Previous work from our laboratory found differences in the length of the branching of the cells; however, we consider that this analysis is insufficient for the complexity that microglia. This work aimed to analyze the morphological changes through fractal analysis of the microglia after a TBI in the motor cortex (M1) depending on the time of day.In a rat model of TBI, from histological samples immunolabelled with Iba-1+ antibody, which recognizes microglia cells, two groups were considered: TBI during the Day group and TBI Night group, each one with its respective control group (n=3) analyzed 24 hours after the trauma. Photos of individual microglia cells in the motor cortex (M1) were taken (n=76). Then they were processed with the ImageJ® and Fiji® Software. Finally, a morphological fractal analysis was applied and we analyzed five features: 1) fractal dimension, 2) lacunarity, 3) density, 4) span ratio, and 5) circularity.In the control groups, statistically significant lower logarithmic values were found for the fractal dimension $t(126) = 2.603$, $p = 0.0103$; and for the density $t(151) = 3.243$, $p=0.0015$, in the Night group compared to the Day group; while the rest of features did not show significant changes. Meanwhile, in the experimental group, statistically significant logarithmic values were found for two parameters: for the fractal dimension, higher significant differences were found in the Night group $p<0.0001$, compared to the Day group $p=0.0058$. For lacunarity, significant differences were found exclusively between the day groups $p<0.0001$, being lower in TBI.We conclude that there is greater homogeneity in the microglia 24h after TBI, exclusively in the day group. This may reflect that there is less branching during the day and therefore suggests greater activation. On the other hand, there is an increase in complexity during the Day and Night

groups; however, this difference is more significant at night, suggesting less activation at night than during the day. This could be partially explained because we have only considered 24h after TBI.

**Disclosures: K. Diaz Duarte:** None. **R. Martinez-Tapia:** None. **F. Estrada-Rojo:** None. **T. Lopez-Aceves:** None. **V. Rodríguez-Mata:** None. **E. Pulido-Camarillo:** None. **A. Perez-Torres:** None. **L. Sanchez-Martinez:** None. **M. De las Casas Cervantes:** None. **F. Espinosa-Becerra:** None. **L. Navarro:** None.

**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.14/T4

**Topic:** C.10. Brain Injury and Trauma

**Support:** CBIR20FEL009
CBIR20IRG003

**Title:** The role of cypin in regulating the ubiquitin-proteasome system

**Authors: *S. GANDU**[1], B. L. FIRESTEIN[2];
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**Abstract:** The ubiquitin-proteasome system (UPS) is a major protein degradation system that maintains cellular homeostasis by regulating protein turnover. In neurons, the UPS plays a significant role in maintaining synaptic plasticity by removing damaged or misfolded proteins. Previous reports indicate that after a traumatic brain injury (TBI), the UPS is dysregulated, affecting synaptic plasticity and neuronal connectivity, ultimately leading to neuronal degeneration. Understanding how the UPS is regulated will potentially help to develop therapies that restrict damage caused by trauma to the brain and prevent further stress on neurons. Preliminary data from our lab suggest that cypin interacts with a subunit of the proteasome. Upon further investigation, we found that cypin overexpression leads to accumulation of ubiquitinated proteins and affects the proteasome activity. We used lentiviral and adeno-associated viral vectors, both *in vitro* and *in vivo*, to overexpress cypin and identify the underlying mechanism that underlies cypin regulation of the proteasome system and protein ubiquitination process. We observed significant changes to the total levels of synaptic proteins and the ubiquitination status of these proteins. We found that cypin promotes a specific type of poly-ubiquitin chain linkage. Thus, we hypothesize that overactivation of cypin can attenuate glutamate-induced excitotoxicity by regulating the UPS and promoting neuronal recovery. Taken together, our results further our understanding of the role of the UPS in neuronal recovery and reveal how cypin can be used as a therapeutic target after brain trauma.

**Disclosures: S. Gandu:** None. **B.L. Firestein:** None.

**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.15/T5

**Topic:** C.10. Brain Injury and Trauma

**Support:** VA Merit Review award 1I01RX001776
the Department of Defense award MR130295

**Title:** Persistent post-surgical allodynia after traumatic brain injury is driven by the pain-facilitating neurons in rostral ventromedial medulla (RVM)

**Authors: *Q. CHEN**, D. J. CLARK;
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**Abstract:** Individuals with histories of traumatic brain injury (TBI) commonly exhibit prolonged recovery after peripheral injuries and experience chronic pain. Our recent data suggest that dysregulated descending pain-facilitating circuits could be involved. We hypothesized that TBI exacerbates pain in response to a subsequent soft tissue injury dependent upon pain-facilitating neurons in the rostral ventromedial medulla (RVM). After mild TBI in mice, we observed bilateral hindpaw allodynia lasting up to 7 days. After recovery, hindpaw incisions in animals with prior TBI displayed sensitization lasting up to 38 days, while incisions in control animals caused only 7 days of sensitization. Furthermore, acute blockade of central but not peripheral mu-opioid receptors (MORs) led to mechanical sensitization in the hindpaws in animals recovered from TBI, while control animals and those with incision alone did not display changes in their pain thresholds after MOR blockade. Increased neuronal activation, marked by c-Fos staining, was observed in RVM in animals recovered from TBI after central MOR blockade. Lastly, microinjecting dermorphin-saporin into the RVM and ablating the RVM MOR+ neurons, which are known for their pain-facilitatory property, attenuated the development of allodynia in animals after TBI and subsequent incisional injury. Acute MOR blockade in dermorphin-saporin-treated animals after they recovered from TBI did not produce mechanical sensitization in the hindpaws. Collectively, these data suggest that dysfunction of the RVM pain-facilitatory neurons is responsible for the slow resolution of pain after peripheral injury in the setting of TBI. The central endogenous opioid system is important to counteract the dysfunctional pain facilitation for the subsequent recovery of pain sensitivity after TBI but not after peripheral injury alone. Identifying ways to enhance endogenous pain control mechanisms may help those with pain after TBI.

**Disclosures: Q. Chen:** None. **D.J. Clark:** None.

**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.16/T6

**Topic:** C.10. Brain Injury and Trauma

**Support:** CNRM-70-8956
USU- PAT-74-3439
CDMRP W81XWH-13-2-0018

**Title:** Comparison of Pathology across Brain Regions after CHIMERA or Repetitive Blast Brain Injury in a Gyrencephalic Animal

**Authors: S. SCHWERIN**[1], B. HUNDITO[2], A. OBASA[2], T. HAIGHT[3], P. CRIPTON[4], K. MCINESS[4], C. WELLINGTON[4], *S. JULIANO[1];
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**Abstract:** The CHIMERA (Closed-Head Impact Model of Engineered Rotational Acceleration) is a relatively new traumatic brain injury (TBI) model; its known effects in a gyrencephalic brain, however, are limited. We previously reported pathological changes following blast exposure in the ferret, which mimic those seen in humans. To determine if different types of brain injury diversely affect brain regions, we compared the effects of CHIMERA with a blast injury. A blast shock wave causes global damage of blood vessels and the blood brain barrier whereas rotational acceleration causes shear strains resulting in neural and axonal damage. Abnormal tau phosphorylation is prevalent during neurodegeneration and the ratio of the tau isoforms 3R to 4R also changes in neurodegenerative diseases and after blast injury in ferret. Our objective was to determine the differences in pathology across the brain after each injury in the ferret. We evaluated mild CHIMERA brain injury using a head interface device at an impact energy of 26-31 J and compared the results with 2 repetitive blast brain injury models: 4B1D - 4 blasts (16-psi) within one hour or 4B4D - 1 blast (16-psi) a day over 4 consecutive days. We used western blot at 4 weeks post injury to assess protein levels in: Prefrontal cortex (PFC), Frontal cortex (Frontal), Cingulate gyrus (CG), Sensorimotor cortex (SM), Occipital cortex-medial and lateral (OCCmed, OCClat), Hippocampus (HIP), Cerebellum-medial and lateral (CERmed, CERlat), and Brainstem (BRSTM). We evaluated proteins related to neurodegeneration: total tau, pTau (phosphorylated tau, CP13), and the 3R and 4R tau isoforms. The blast injuries generally caused greater pathological protein expression across brain regions compared with CHIMERA. However, the CHIMERA resulted in greater expression of phosphorylated tau and total tau proteins in the PFC; total tau in the HIP; 3R isoform in the BRSTM; and the 4R isoform in the CERmed. When comparing between the 2 repetitive blast models, 4B4D produced greater expression of all the pathological proteins in the PFC, HIP, CERmed, CERlat, and BRSTM with a few exceptions. The 4B1D produced greater pathological protein expression in the CG, Frontal, OCCmed, SM cortices, also with a few exceptions. These findings demonstrate that the CHIMERA and repetitive blast injury resulted in different and distinct regional neuropathological tau protein changes. The repetitive blast resulted in greater and more widespread elevations in pathological proteins, whereas the CHIMERA injury revealed

select brain regions where tau-related proteins were more highly elevated than following blast exposure.

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**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.17/T7

**Topic:** C.10. Brain Injury and Trauma

**Support:** CNRM-70-8956
USU-PAT-74-3439
CDMRP W81XWH-13-2-0018

**Title:** Persistent structural deficits in cerebellar cortex and white matter tracts following combination TBI in a gyrencephalic animal model

**Authors: *K. MANETZ**[1], N. BREEHL[2], A. OBASA[3], M. CHATTERJEE[3], B. HUNDITO[1], S. C. SCHWERIN[3], S. L. JULIANO[3];
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**Abstract:** Traumatic brain injury (TBI) is a common source of persistent morbidity in both military and civilian populations, with blast injury being one of the primary drivers of TBI in veterans of the Afghanistan and Iraq wars. In order to create a more realistic TBI model in a gyrencephalic animal (the ferret), we used a combination of injuries consisting of multiple primary blast waves interspersed with rotational head injuries (CHIMERA) over a period of 2 weeks. The role of the cerebellum in ongoing TBI pathology is currently understudied and could be a source of persistent pathology. Ferrets were exposed to varying amounts of stress and sacrificed at 4 weeks and 6 months post injury. Antibodies directed against Calbindin, Myelin Basic Protein (MBP), IBa1, GFAP, and SOX2 characterized cerebellar architecture, including Purkinje cells and their axons, Bergmann glia, astrocytes, and microglia. Subjects at 4 weeks and 6 months post injury showed diffuse loss of Purkinje cell soma and decreased dendrite density, with the greatest loss noted in animals sacrificed at 6 months and exposed to stress. Marked variation in the degree of Purkinje cell soma loss was noted between injured animals within the same cohorts, indicating a role for intrinsic protective factors. The greatest decrease in Purkinje Cell/Calbindin expression was seen in the superior and posterior lobules with greater pathology in medial cerebellar regions. Bergman glial architecture was largely maintained in injured animals irrespective of the degree of Purkinje cell loss. A substantially decreased thickness of the SOX2+ cell population occurred in the Purkinje cell layer in the injured animals compared to control/sham. Cerebellar regions with greater amounts of damage showed less SOX2+ cells

compared to regions with more intact Calbindin staining. We also analyzed the Calbindin immunoreactivity in Purkinje cell axons and its colocalization with MBP. A one way ANOVA showed significantly decreased colocalization of MBP and Calbindin at 4 weeks ($p = 0.0314$) and 6 months ($p = 0.0021$) post injury, especially in the white matter tracts of the posterior and superior lobules of injured animals compared to control, indicating an interruption of Purkinje cell axons. Given that Purkinje cells are the only output cell of the cerebellum, axonal disruption exists as a potential mechanism for persistent functional deficits following combination TBI. These findings as a whole indicate ongoing and evolving cerebellar pathology following combination TBI.

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**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.18/T8

**Topic:** C.10. Brain Injury and Trauma

**Support:** CNRM-70-8956
USU- PAT-74-3439
CDMRP W81XWH-13-2-0018

**Title:** Prion Protein expression shows variable increases across the brain after traumatic brain injury.

**Authors: *B. HUNDITO**[1], S. C. SCHWERIN[2], M. CHATTERJEE[5], K. MANETZ[3], S. L. JULIANO[4];
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**Abstract:** Traumatic Brain Injury (TBI) comprises the majority of injuries occurring in military conflicts. Several recent advances aid in the detection of biochemical markers for TBI in service members exposed to head injuries. These include different forms of tau, including phosphorylated tau, and the isoforms 3R and 4R. In this study, we evaluate Prion protein, a glycoprotein found in the extracellular membranes of neurons in the central nervous system (CNS) and postulated to be aberrantly expressed in TBI. We studied changes in protein expression through Western Blot analysis in Ferrets. Ferrets, as the smallest mammal with a gyrencephalic neocortex are an excellent model to study TBI. We evaluate alterations in the expression levels of Prion Protein after two different types of injuries: explosive Blast and the Closed Head Injury Model of Engineered Rotation and Acceleration (CHIMERA) at 4 weeks

post injury. This important analysis will aid in understanding both the global injury effect of each injury in the brain as well as and the distinction between them. We assessed different regions of the Ferret brain: including Frontal Cortex, Prefrontal Cortex, Primary Somatosensory Cortex, Occipital Lobe, Hippocampus, and Brainstem and across different 3 temporal distribution of injuries: 1 blast per day for 4 days (4B4D) compared to 4 blast injuries in one 1 day (4B1D), a single CHIMERA injury. In general, Prion protein increased expression in Blast injuries compared to CHIMERA in all brain regions except the Brainstem. More specifically, the expression of Prion Protein in relation to the temporal distribution of Blast injuries was more variable. Animals receiving multiple blast injuries over 1 day (4B1D) had significantly more expression of Prion Protein in the Frontal and Primary Somatosensory regions than the 4B4D animals, receiving single blast injuries over 4 days. In contrast, 4B4D animals exhibited more Prion Protein expression in the Prefrontal Cortex and the Hippocampus than the 4B1D animals. Other neocortical regions showed similar Prion Protein expression for both delivery time frames (4B4D and 4B1D). Overall, our work demonstrates that Prion Protein expression increases in the brain after different types of Traumatic Brain Injury and varies in extent across the brain. Blast injury generally resulted in greater Prion Protein expression than CHIMERA injury. This also suggests that Prion Protein may contribute to the long term pathology associated with TBI, including difficulties with sleep, depression, and headache.

**Disclosures: B. Hundito:** None. **S.C. Schwerin:** None. **M. Chatterjee:** None. **K. Manetz:** None. **S.L. Juliano:** None.

**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.19/T9

**Topic:** C.10. Brain Injury and Trauma

**Support:** United States Defense Health Agency Program in Brain Injury and Disease Prevention, Treatment, and Research (HU0001-22-2-0002).

**Title:** Neuronal Tau Pathology Worsens Late Phase White Matter Degeneration After Traumatic Brain Injury in Transgenic Mice

**Authors: *F. YU**[1], D. IACONO[2,3,4,5], D. P. PERL[3,4,6], C. LAI[5,6], J. GILL[7], T. Q. LE[1], P. LEE[3,5,6], G. SUKUMAR[1], R. C. ARMSTRONG[1,6];
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**Abstract:** Traumatic brain injury (TBI) causes diffuse axonal injury which can produce chronic white matter pathology and subsequent post-traumatic neurodegeneration with poor patient

outcomes. Tau modulates axon cytoskeletal functions and undergoes phosphorylation and mis-localization in neurodegenerative disorders. The effects of tau pathology on neurodegeneration after TBI are unclear. We used mice with neuronal expression of human mutant tau to examine effects of pathological tau on white matter pathology after TBI. Adult male and female hTau.P301S (Tg2541) transgenic and wild type (Wt) mice received either moderate single TBI (s-TBI) or repetitive mild TBI (r-mTBI; once daily x 5), or matched sham procedures. Acutely, s-TBI produced more extensive axon damage in the corpus callosum (CC) as compared to r-mTBI. After s-TBI, significant CC thinning was present at 6 weeks and 4 months post-injury in Wt and transgenic mice, with homozygous tau expression producing additional pathology of late demyelination. In contrast, r-mTBI did not produce significant CC thinning except at the chronic time point of 4 months in homozygous mice, which exhibited significant CC atrophy (-29.7%) with increased CC microgliosis, but not astrogliosis. Serum biomarker quantification demonstrated neurofilament light detection of early axonal damage one day post-injury in Wt and homozygous mice. At 4 months, high tau and neurofilament in homozygous mice implicated tau in chronic axon pathology. Conclusions: Neuronal tau pathology differentially exacerbated CC pathology based on injury severity and chronicity. Ongoing CC atrophy from s-TBI became accompanied by late demyelination. Pathological tau significantly worsened CC atrophy during the chronic phase after r-mTBI.

**Disclosures: F. Yu:** None. **D. Iacono:** None. **D.P. Perl:** None. **C. Lai:** None. **J. Gill:** None. **T.Q. Le:** None. **P. Lee:** None. **G. Sukumar:** None. **R.C. Armstrong:** None.

**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.20/T10

**Topic:** C.10. Brain Injury and Trauma

**Support:** W81xWH1910309
R01AG075092
K01-AG056673
R56-AG066782-01

**Title:** Cell-type-specific alterations of BAG3 and tau phosphorylation in mouse and human brains with traumatic brain injury

**Authors: *N. SWEENEY**[1], T. KIM[2,1], C. MORRISON[1], L. LI[1], J. LIANG[1], D. ACOSTA[1], S. CHEN[2,1], H. HUANG[3], J. FITZGERALD[1], K. KARELINA[5], C. E. BRAY[1], Z. M. WEIL[5], G. HUANG TAN[1], D. SCHARRE[4], G. E. SERRANO[6], T. G. BEACH[6], J. P. GODBOUT[1], O. KOKIKO-COCHRAN[1], T. SAITO[7], T. SAIDO[7], H. FU[1];
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Body Donation Program, Banner Sun Hlth. Res. Inst., Sun City, AZ; [7]Neurocognitive Sci., Brain Sci. Inst, RIKEN, Wako, Japan

**Abstract:** People living with Traumatic brain injury (TBI) experience an increased incidence of Alzheimer's disease (AD) and related dementias (ADRD), which tau pathology is a major pathological hallmark. Recently, we identified BCL2 associated athanogene 3 (BAG3), a facilitator of autophagy that controls tau homeostasis and intrinsic vulnerability to tau pathology. We hypothesize that BAG3 decreases in cells vulnerable to tau pathology but increases in cells resistant to tau accumulation in mouse and human brains with TBI. To test this hypothesis in mouse models with TBI, we utilized the controlled cortical impact (CCI) model (velocity 3.00 m/s, depth 0.8 mm, dwell time: 200ms). The CCI model induced tau hyperphosphorylation, gliosis, and cognitive deficits in wild type (C56BL6/J), human tau knock-in, and double-knock in mice (hAPP/hTau). Using immunofluorescent (IF) staining of fixed mouse brain floating sections, we measured the protein level of BAG3 in cells with PHF1 (pS396/S404 tau) positive staining and adjacent PHF1-negative cells. We found that neurons (SATB2+) and oligodendrocytes (Olig2+) with higher BAG3 level had lower PHF1+ phosphorylated tau (ptau) accumulation than cells with low BAG3 level. We also found that BAG3 level is upregulated in cells resistant to ptau accumulation, such as astrocytes (GFAP+ cells) and microglia/macrophage (P2RY12+ cells), compared to sham controls.To validate our findings in human post-mortem brain sections from the inferior parietal lobe (IPL, a major region affected in TBI), we used IF staining to evaluate the protein level of BAG3 and PHF1 in multiple disease conditions (AD, TBI, and AD with TBI) and control brains. In accordance with our mouse data, we observe that neurons and oligodendrocytes with higher BAG3 level have lower PHF1+ ptau accumulation than cells with lower BAG3 level. We also show that GFAP+ and P2RY12+ cells with resistance to ptau accumulation exhibit increased BAG3 levels across disease conditions. In conclusion, TBI reduces the specific expression of BAG3 in neurons and oligodendrocytes in mouse models and human post-mortem brain tissue, contributing to pathological tau accumulation in these cell types. TBI also promotes upregulation of BAG3 in astrocytes and microglia, which may contribute to their resistance to ptau accumulation. Future studies will investigate the molecular mechanism underlying tau clearance by BAG3 and how TBI affects this process.

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**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.21/U1

**Topic:** C.10. Brain Injury and Trauma

**Title:** Examining Neuropathological Responses in Woodpeckers to Gain Insights into Chronic Traumatic Encephalopathy (CTE)

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**Abstract:** Chronic traumatic encephalopathy (CTE) is a debilitating neuropathic condition characterized by the accumulation of hyperphosphorylated tau within the brain. CTE is often the result of repeated mild traumatic brain injuries or acceleration/deceleration brain injuries and can result in severe symptoms such as depression, memory loss, and impulsivity over time. Despite its prevalence and associated severe consequences, very few treatment options exist. To more accurately approximate clinical scenarios, we require a greater diversity of animal models for effectively simulating CTE. Here, we adopt a novel approach of leveraging wild woodpeckers' unique drumming and nest excavation behaviors that result in exposure to frequent high-deceleration forces on the brain as a model for identifying natural mechanisms against CTE. Our investigation focuses on two crucial areas: (i) identifying the presence of neuropathological markers associated with CTE, and (ii) examining the transcriptome of the brain and meninges—both of these elements have been shown to be significantly affected by traumatic brain injury in humans and other animal models. Comparative analysis revealed that Downy Woodpeckers (*Dryobates pubescens*) have fewer brain regions with hyperphosphorylated tau (pTau S404), an early CTE-related neuropathy marker, compared to the non-drumming Tufted Titmouse (*Baeolophus bicolor*). The connection between neuroinflammation and CTE remains understudied. Thus, we also measured neuroinflammation-associated transcripts such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and Substance P across the brains of four bird species, providing a nuanced understanding of the neuropathological responses to high-impact forces. Concurrently, we are surveying species- and sex-specific transcriptomics of woodpecker and titmouse meningeal tissue, aiming to identify distinct regulatory molecular pathways associated with neuroprotection. This research has the potential to elucidate how woodpeckers' unique adaptations to high-impact forces can offer valuable insights into the biology of CTE. The findings may open up new avenues for exploring CTE prevention and intervention strategies, thus allowing for an improved and complementary model of CTE research.

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**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.22/U2

**Topic:** C.10. Brain Injury and Trauma

**Support:** DOD Peer Reviewed Alzheimer's Research Program (US) (AZ180043)
VA ORD BLR&D CSR&D (I01 BX004313-01A1, Collaborative Merit Review for TBI Research Program)
VA ORD (BLR&D Director Service program (UFR- 002-18F))

**Title:** Application of a sensitive and high-resolution analysis approach highlights heterogeneous behavior and histology in mice exposed to repetitive low-intensity primary blast wave exposure

**Authors: *A. ZUCKERMAN**[1,2], H. R. SIEDHOFF[1,2], A. BALDERRAMA[1,2], R. LI[1,2], J. CUI[1,2], Z. GU[1,2];
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**Abstract:** Primary low-intensity blast (LIB) exposure frequently causes mild traumatic brain injury (mTBI) in military and civilian settings. Blast-induced mTBI is known as an "invisible injury", as neuroimaging often detects no abnormalities in the acute and subacute phases. Yet, brain damage occurs at the nanoscale level, and results in behavioral adverse. In some cases, those adverse behaviors persist for months to years following injury. This heterogeneous response complicates clinical diagnosis, urging researchers transition from using "classical" research methods (i.e., group-level comparisons). Group-level comparisons for mild conditions are low-resolution and often insensitive to detect the consequences of blast-induced mTBI. Moreover, while pre-clinical researchers compare behaviors and neuropathological outcomes at the group level between blast-exposed and unexposed animals, clinicians evaluate patients individually. The purpose of this research was to implement a within-individual correlation analysis approach to evaluate male and female mice with repetitive LIB exposure using the open field "Missouri Blast" model. Three months post-exposure, the mice were subjected to a series of behavioral tests measuring daily living, learning and memory, and anxiety-related behaviors. The brains were then collected and Tau-related proteins were analyzed using immunohistochemistry. Data analysis focusing on injured mice individually revealed significant behavioral and histological differences. Differences extended beyond the individual level, with genotype, sex, and blast exposure significantly affecting learning capabilities. Immunohistochemistry revealed a related increase of phosphorylated-Tau in the CA3 subregion of the hippocampus. In conclusion, the use of individual evaluation methods increases our understanding of the heterogeneity of blast-induced mTBI pathologies. Applying the high-resolution and sensitive individual analyses in preclinical settings can improve the clinical translational value of findings.

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**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.23/U3

**Topic:** C.10. Brain Injury and Trauma

**Support:** DOD Peer Reviewed Alzheimer's Research Program (US) (AZ180043)
VA ORD BLR&D CSR&D (I01 BX004313-01A1, Collaborative Merit Review for TBI Research Program)
VA ORD (BLR&D Director Service program (UFR- 002-18F))

**Title:** Mice Exposed to Open-Field Low-intensity Blast Revealed Position-Dependent Blast Effects on Molecular Signatures and Neurobehavioral Deficits

**Authors: *Z. GU**[1,2], M. JACKSON[2], S. CHEN[2,1], P. LIU[2], H. SIEDHOFF[2], A. BALDERRAMA[2,1], C. LI[2], A. ZUCKERMAN[2,1], C. JOHNSON[3], M. GREENLIEF[2], G. SUN[2], I. CERNAK[4], J. CUI[2];
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**Abstract:** The neurological consequences of combat blast-induced neurotrauma (BINT) pose important clinical concerns for military service members and veterans. Previous studies showed low-intensity blast (LIB) results in BINT with multifaceted changes in mice exposed to open-field blast (OFB) in the prone position. Although the prone position is natural for rodents, experimental models of blast injuries using this position do not represent common scenarios of humans standing while being exposed to blast during deployment or military training. In this study, we designed a 3-D printed device in which mice were held in the upright position during OFB. Quantitative proteomics and multiple bioinformatic approaches were used to analyze brain tissue taken from representative brain subregions during the acute post-OFB injury phase. We identified 1) region-specific blast-induced proteome changes, which were significantly and differently influenced by animal positioning (upright vs. prone): animals receiving OFB in the upright position showed more significant protein alterations in the cortex and cerebellum, and less significant in the striatum as compared to those in the prone position; 2) we detected OFB-induced synapse- and mitochondrion-related brain damage in both positions; and 3) some pathways were differentially regulated due to the two positions, e.g., differences in autophagy and sirtuin pathways. Furthermore, assessment using the automated home-cage monitoring system revealed position-dependent differences in learning and cognitive flexibility at 30 days post-OFB injury. In sum, this study unveiled position-dependent differences in molecular signatures, protein networks, and associated cognitive flexibility and learning defects during the acute and sub-acute phases of OFB. This study illustrates the importance of addressing positional dependence of biological responses to blast, aiming to better align experimental research models with militarily and clinically relevant scenarios, thus providing translational value to develop strategies to prevent, mitigate and treat primary blast injuries.

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**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.24/U4

**Topic:** C.10. Brain Injury and Trauma

**Support:** 1 RO1 HL139708-01A1
1 RO1 HL153140-01

**Title:** Novel, interesting, surprising and useful properties of a panel of NF-L, NF-M and NF-H monoclonal antibodies.

**Authors:** *G. SHAW[1], I. MADORSKY[2], M. JORGENSEN[2], ***G. SHAW**[1], S. RANA[3], D. FULLER[3];
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**Abstract:** Neurofilament light protein (NF-L) is detected at informative levels in blood, CSF and other fluids associated with a variety of neurodegenerative states using assays from Uman Diagnostics, Quanterix and others. We show that both monoclonal antibodies used in these assays bind to a peptide in the middle of the NF-L “Coil II” sequence. We made a novel panel of monoclonal and polyclonal antibodies to this region. Surprisingly, all such antibodies do not recognize typical neurofilament rich profiles in healthy neurons and their processes in sectioned material, instead recognizing a few rare profiles which have the appearance of neurodegeneration. Following a mid-cervical spinal cord contusion injury in rats, these antibodies reveal numerous strongly stained beaded, sinusoidal or discontinuous nerve fibers in regions expected to contain compromised processes. The unmasking of the degeneration specific epitopes can be mimicked by treating sections of healthy tissue with proteases, which results in previously unreactive NF-L containing profiles becoming strongly reactive with this specific type of NF-L antibody. We also show that the NF-L Coil II region contains many more epitopes hidden in healthy neurofilaments but revealed on degeneration and that the homologous Coil II regions of NF-M and NF-H also contain epitopes hidden in healthy cells but revealed on degeneration. We propose that the hidden epitopes are part of functionally important binding sites important for neurofilament assembly. This panel of novel reagents are robust, excellent and specific markers of neurodegeneration of wide utility in future studies of CNS disease and injury.

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**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.25/U5

**Topic:** C.10. Brain Injury and Trauma

**Support:** NIH 1R21NS123814
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**Title:** Apoe4 leads to persistent astrocytic reactivity and dysfunction to adulthood after neonatal hypoxia-ischemia

**Authors: *R. CHAVEZ-VALDEZ**[1], M. ST. PIERRE[2], M. NUGENT[2], K. CARLIN[4], S. DUCK[2], M. NAZARETH[5], A. FASSINGER[2], C. PINTO[6], G. ELMORE[2], S. NASSAR[2], F. J. NORTHINGTON[7], L. MARTIN[3];
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**Abstract:** Human apolipoprotein E allele ε4 (ApoE4), a major risk factor for neurodegenerative disorders (i.e. AD), is associated with reduced temporal cortex thickness and hippocampal volume predicting lower working memory in healthy children. Astrocytes, the primary source of ApoE4 in the brain, are central in the pathophysiology following neonatal HI, but whether ApoE4 alters these responses is unknown. We hypothesize that ApoE4 leads to persistent astrocytic reactivity and dysfunction to adulthood in response to neonatal HI characterized by a pro-inflammatory state and impaired glutamate recycling capacity resulting in early neurodegeneration and cell death. Cerebral HI injury (Vannucci model) was produced on postnatal day (P)10 ApoE $^{-/-}$ mice genetically humanized by global ApoE ε3 or ε4 allele knock-in. Controls were HI and sham wildtype (wt) C57BL6 mice and sham ApoE mice. Hippocampus of survivors was interrogated at 6 mo of age for RNAseq and a combination of immunoblotting and IF-IHC with Imaris processing for GFAP, EAAT2 (GLT1), HK1, TNF-α, and Ser396 phosphorylated Tau$^{+}$ cells. 6 mo old HI-ApoE4 hippocampus had upregulated RNA levels for astrocyte reactivity markers (RNAseq, FDR-p-value <0.05 vs. sham), including the C1q-C3 cascade linked to chronic astrocytic activation. Increased GFAP protein levels in HI-ApoE4 hippocampus (vs. sham) correlated with rise in ApoE4 levels. Astrocyte number and complexity were also increased. Sholl analysis showed more branching mainly in the CA3 of HI (blue) ApoE4 mice vs. sham (maroon) or hypoxia-alone (contralateral to HI, green), complexity that directly correlated with the number of dying pTau$^{+}$ cells. Astrocytic pro-inflammatory gene profile in RNAseq was supported by TNF-α expression within reactive astrocytes. Decreased glutamate transporter EAAT2 (GLT1) gene expression and protein levels occurred along with profound decrease in hexokinase 1 (HK1), an enzyme essential for ATP-dependent EAAT

function. ApoE4 leads to persistent reactivity and dysfunction of hippocampal astrocytes to adulthood after neonatal HI. This dysfunction is characterized by a pro-inflammatory state and decreased glutamate recycling capacity, which may lead to ongoing excitotoxicity and cell death and early neurodegeneration, beyond injured non-ApoE4 carriers. We propose chronic astrocytic reactivity and dysfunction as a central mechanism involved in suspected late life consequences of perinatal brain injury in ApoE4 carriers.

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**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.26/U6

**Topic:** C.10. Brain Injury and Trauma

**Title:** Uninterrupted in vivo cerebral microdialysis measures of the acute neurochemical response to a single or repeated concussion in a rat model combining force and rotation

**Authors: *I. MASSE**[1], L. MOQUIN[2], C. BOUCHARD[1], A. P. GRATTON[2], L. DE BEAUMONT[3];
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**Abstract:** There are marked alterations in extracellular amino acid levels following a concussion, contributing to delayed neuronal damage, but the consequences of repeated concussions prior to complete recovery are less known. This study investigated in adult rats, acute changes from a single or repeated concussive trauma. A weight-drop injury model and in vivo cerebral microdialysis were used. Primary outcome includes amino acid levels and secondary outcome includes righting time. Samples were taken in 10 min increments for 60 min prior to, during and for 60 min following impact, and analyzed for glutamate, GABA, taurine, glycine, glutamine, and serine using HPLC. For repeated concussion cases, a second injury was induced 60 min after the first, and 6 additional samples were collected for 60 min. Following the first concussion, glutamate, taurine, and glycine levels as well as righting times and excitotoxic indices were significantly increased compared to sham injured animals. Following the second concussion, glutamate and taurine levels were significantly increased again, albeit only halfway, compared to sham injured animals. Righting times took significantly longer after the second concussion, while glycine levels were comparable to sham injured animals. These results suggest that single and repeated concussion induce an acute increase in certain amino acids. While these changes were less pronounced following a second impact, neurological symptoms as seen

through righting times had worsened, suggesting acute cumulative effects of repeated concussion on neurological function.

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**Poster**

**PSTR021. Brain Injury and Neurodegeneration: Cellular and Molecular Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR021.27/U7

**Topic:** C.10. Brain Injury and Trauma

**Support:** NRF-2020R1C1C1006659
KIRAMS-No. 50531-2023

**Title:** Single-cell RNA-seq analysis of mice brain following cranial irradiation

**Authors:** Y. CHOI, H.-J. LEE, ***Y. SON**;
Korea Inst. of Radiological and Med. Sci. (KIRAMS), Seoul, Korea, Republic of

**Abstract:** Though cranial irradiation (IR) is often used to treat brain tumors, it could result in long-lasting side effects, including cognitive impairment and depression. The mechanism of the brain dysfunctions after IR is not well understood, chronic neuroinflammation is among the underlying mechanisms. Single-cell RNA sequencing (scRNA-seq) was used to investigate cell-type specific gene expression in brain from sham (0 Gy)-irradiated and 10 Gy-irradiated mice. Using marker genes, we uncovered the presence of three of microglial subpopulations. Among them, we detected the number of one subtype is reduced following cranial IR. Differentially expressed genes (DEGs) of microglia is selectively analyzed between sham- and 10 Gy-irradiated group. Gene ontology analysis suggests that inflammatory response-related pathway is up-regulated compared to sham-irradiated group. Our results indicate that changes in microglial phenotypes are involved in radiation-induced brain dysfunction, which needed further studies to unveil detailed variable gene expression of microglia following IR exposure.

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**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.01/U8

**Topic:** C.11. Spinal Cord Injury and Plasticity

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Additional support was provided by the Center for Computation and Visualization (CCV), and computing hardware supported by NIH Office of the Director Grant S10OD025181.

**Title:** Characterizing perceptual differences in supralesional EES-evoked sensations in persons with complete spinal cord injury.

**Authors: *S. R. PARKER**[1], J. S. CALVERT[1], L. N. GOVINDARAJAN[2], R. DARIE[1], E. SHAAYA[4], P. MIRANDA[1], Z. L. GOKASLAN[4], L. J. RESNIK[5], T. SERRE[2], J. S. FRIDLEY[4], D. A. BORTON[3];
[1]Sch. of Engin., [2]Cognitive, Linguistic, and Psychological Sci., [3]Brown Univ., Providence, RI; [4]Dept. of Neurosurg., Rhode Island Hosp., Providence, RI; [5]Res. Dept., Providence VA Med. Ctr., Providence, RI

**Abstract:** Spinal cord injury (SCI) is a debilitating condition, often resulting in chronic impairment of sensorimotor function, and affects between 249,000 and 363,000 Americans. Recent preclinical and clinical research has indicated that epidural electrical stimulation (EES) of the spinal cord below the level of injury can restore motor ability. While this represents a novel potential treatment for chronic SCI, sensation below the lesion remains impaired. Previous studies have established that the simultaneous application of peripheral sensory feedback improves functional performance of people using prosthetic upper- and lower-limbs, and that EES to the intact spinal cord can evoke sensation. Crucial to the effective application of sensory EES is an understanding of how changes in the applied stimulation are transformed by ascending neural circuits, leading to modified neural representations evoked by stimulation and eventual perception. As part of an ongoing clinical trial (NCT04302259), we implanted an epidural spinal cord stimulation array in one participant spanning T1-T3, above the injury site (T4). During the 10-day inpatient phase of the study, we assessed the diversity and quality of stimulation evoked percepts across a large EES input space. Evoked sensations emanated from similar regions across participants, chiefly from dermatomes projecting to spinal levels underlying the implant. We assessed the sensitivity of stimulus detectability and discriminability of changes in EES parameters. We identified expected sigmoidal detectability relationships for stimulation

amplitude and pulse width, and identified detectability improvements for a narrow band of stimulus frequencies. Finally, using a novel participant-controlled stimulation interface, we examined the way in which participants navigated through parameter-space in a perception matching task. We found that participants "trade-off"stimulus dimensions to achieve perceptibly identical evoked sensations. These tasks enabled us to gauge the diversity, sensitivity, and identifiability of EES evoked sensations. Understanding these complex relationships will enable future sensory restorative neuroprostheses to better encode perceptual information, readying this technology to improve the lives of people living with complete SCI.

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**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.02/U9

**Topic:** C.11. Spinal Cord Injury and Plasticity

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VA Merit Review Award I01RX002835
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NIH Fellowship K23HD102663
VA RR&D A9263A-S Research Career Scientist Award

**Title:** Translesional stimulation replaces lost sensorimotor function in persons with paraplegia

**Authors: *J. S. CALVERT**[1], S. R. PARKER[1], L. N. GOVINDARAJAN[2], R. DARIE[1], E. SHAAYA[3], R. SOLINSKY[6], L. M. DEL VALLE[1], P. MIRANDA[1], J. JANG[2], E. TIWARI[1], S. SYED[3], R. M. VILLALOBOS[4], L. M. AGUIAR[5], H. TANG[7], S. MCPHERSON[7], W. XUE[7], A. G. CARAYANNOPOULOS[4], A. A. OYELESE[3], Z. L. GOKASLAN[3], A. K. BANSAL[7], L. J. RESNIK[8], T. SERRE[2], J. S. FRIDLEY[3], D. A. BORTON[1];
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**Abstract:** Spinal cord injury (SCI) often results in permanent impairment of sensory, motor, and autonomic function. Foundational preclinical and clinical research has demonstrated that epidural electrical stimulation (EES) applied over the lumbosacral spinal cord can restore

locomotion following SCI and enable voluntary control of previously paralyzed musculature. However, EES below the SCI lesion does not restore sensation, preventing the execution of finely tuned movements. We hypothesized that translesional EES could provide useful sensory feedback during EES-enabled motor tasks in humans with sensorimotor complete SCI. Here, we present first-in-human results from two participants with sensorimotor complete SCI in a clinical trial (NCT04302259) demonstrating simultaneous somatosensory feedback and lower extremity motor activation enabled by two EES paddles implanted rostral and caudal to the SCI lesion, respectively. We determined optimal EES parameters by leveraging modern deep learning methods to establish stable mappings between EES inputs and sensorimotor outputs. Through self-directed, manual stimulation control, participants identified additional EES parameters that elicited qualitatively and quantitatively distinct perceptions. Utilizing these optimized stimulation parameters, we applied spatiotemporally modulated EES rostral to the lesion synchronized with leg movement, enabling participants to accurately report leg position. We then simultaneously applied spatiotemporal EES rostral and caudal to the lesion to enable intentional participant-directed control over leg movements with sensory feedback while supine. Additionally, translesional EES provided sensory feedback during functionally relevant phases of EES-enabled treadmill stepping (i.e., toe-off and heel strike), which the participants used to identify foot strike consistently and accurately. Through the translesional EES approach, we demonstrate that EES applied above the SCI lesion produces sensory percepts that can be used by participants with complete SCI to encode lower extremity limb position, with and without neuromodulation-enabled motor activation. Our translesional EES framework represents the first steps towards developing a next-generation sensorimotor neuromodulation approach to improve the quality of life in individuals with neural dysfunction.

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**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.03/U10

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** DARPA Contract D15AP00112
DARPA Contract D19AC00015
IRP Grant P152
Brown University Presidential Fellowship

**Title:** Spinal cord stimulation and limb movements differentially affect the primary somatosensory cortex

**Authors: *R. DARIE**[1], *R. DARIE[2], D. A. BORTON[1,3,4,5];
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**Abstract:** Spinal cord stimulation (SCS) is a neuromodulation technique commonly used as a treatment for chronic pain. Researchers have recently reported the use of SCS to deliver sensory feedback from a prosthesis. However, the most common perceptual effect of SCS is paresthesia. We hypothesized that this altered perception is accompanied by altered electrophysiological activity in the somatosensory cortex. Here, we describe differences in size and spectral makeup of somatosensory potentials evoked by naturalistic (lower limb movements) and artificial (SCS) stimuli in awake nonhuman primates. We implanted two animals with epidural spinal stimulating electrodes and intracortical recording electrodes in area 2 of S1. The animals were trained to passively allow their lower limbs to be positioned by a robotic apparatus while trains of SCS either replaced or accompanied the limb movement.
Movement and SCS, separately, correlated with evoked potentials (EPs) that were similar in size, measured via the rectified area-under-the-curve (rAUC). We hypothesized that applying SCS during movement would engage gating mechanisms that diminish the cortical responses, compared to identical pulses delivered at rest. In contrast, we observed that simultaneous movement and SCS elicited potentials with larger rAUCs than either stimulus alone. These results suggest that SCS can produce neural input that coexists with ongoing sensory activity.
Next, we measured the spectral power of EPs in the following frequency bands: beta (15 - 30 Hz), gamma (30 - 60 Hz), high-gamma (60 - 120 Hz) and “spike-related” (120 - 1000 Hz). The magnitude of the SCS-evoked spectral peaks was proportional to stimulation amplitude across all bands. In contrast, movement-evoked power in the beta band was lower than at baseline, a phenomenon known as event-related desynchronization (ERD). These results suggest that SCS may disrupt movement-related beta-band activity.
Our results identify neurophysiological dimensions along which the effects of SCS are similar or distinct from the effects of natural movements. Future studies should identify perceptual correlates of these observations, towards developing stimulation strategies that deliver naturalistic perceptual feedback.

**Disclosures: R. Darie:** None. **R. Darie:** None. **D.A. Borton:** None.

**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.04/V1

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** NIH Grant NINDS RO1 NS119475
Craig H. Neilsen Foundation 647897

**Title:** Are restorative effects of transcutaneous spinal cord stimulation retained?

**Authors: T. E. GRAY**, N. YAKAS, D. C. MALLOY, *M.-P. COTE;
Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

**Abstract:** Spasticity emerges in over 75% of spinal cord injured (SCI) individuals contributing to a range of debilitating symptoms including increased muscle tone, involuntary movements, and hyperactive reflexes. Transcutaneous spinal cord stimulation (tSCS) has been shown to decrease spasticity in SCI individuals. Similarly, we have previously shown that tSCS can restore reflex modulation and spinal hyperexcitability to improve spasticity and increase motor output after SCI in rodents. However, it remains to be determined whether improvements in spasticity are retained without further stimulation sessions. In this study, we aim to evaluate the persistence of these effects once tSCS is discontinued.
Adult female Sprague-Dawley rats received a severe T9 contusion injury (250 kdyn) and were randomly assigned to the stimulated group (tSCS) or sham group. tSCS was administered starting 5d post-SCI for 6 weeks. Stimulation was administered 5 days per week with intensities alternating between at supra-(1.2T) and subthreshold (0.8T) in alternating 3-minute bouts (1 ms pulses, 0.2 Hz) for 18 minutes. A retention period of 4 weeks followed where no tSCS or sham treatment was administered. Spasticity was evaluated from the EMG activity in hindlimb muscles in response to ankle stretches in the awake animals throughout the study. Other behavioral measures for movement and sensation included BBB and dorsal Von Frey tests pre-injury (baseline), pre-treatment, mid-treatment, post-treatment, and post-retention period. Terminal experiments to examine rate modulation and presynaptic inhibition of the H-reflex were performed at the end of the experimental timeline after 6 weeks of tSCS and 4 weeks of retention. We found that functional and electrophysiological improvements in spasticity and hyperreflexia following 6 weeks of repeated tSCS were maintained to the end of the experimental timeline. Together, our results suggest that the effects of tSCS persist following a 4-week retention period and that functional benefits are retained after discontinuation of tSCS.

**Disclosures: T.E. Gray:** None. **N. Yakas:** None. **D.C. Malloy:** None. **M. Cote:** None.

**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.05/V2

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** National Institute of Neurological Disorders R01 NS119475
Craig H. Neilsen Foundation (647897)

**Title:** Repeated transcutaneous spinal cord stimulation improves spasticity when initiated in the chronic phase of spinal cord injury

**Authors: *N. YAKAS**, D. C. MALLOY, M.-P. COTE;
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**Abstract:** Approximately 75% of individuals with a spinal cord injury (SCI) develop spasticity. Unfortunately, many of the current pharmacological treatment options available for patients have serious side effects and limit motor recovery. Recent studies utilizing transcutaneous spinal cord stimulation (tSCS) after SCI have demonstrated its feasibility and potential to treat spasticity. However, animal studies investigating stimulation-based therapies have only focused on efficacy when treatment is administered in the acute phase of injury which is less clinically relevant. Our previous work has demonstrated that repeated tSCS in the acute phase of injury improves spasticity and increases membrane-bound KCC2. However, additional rodent studies are needed to bolster available information regarding tSCS's therapeutic potential and further solidify the efficacy of repeated tSCS after SCI to improve spasticity in the chronic phase of injury. The objective of this study is to investigate the impact of repeated tSCS on spasticity and the mechanisms underlying improvement using female Sprague-Dawley rats with a chronic severe (250kDa) T9 contusion injury. Animals (n=18) were randomly assigned into one of two experimental groups: chronic SCI+tSCS (n=9) or chronic SCI+sham stimulation (n=9) as a control. Stimulation sessions began 4-weeks post-injury (5 days/week for 6 weeks). Rate modulation and presynaptic inhibition of the plantar H-reflex were used in a blinded terminal experiment to assess spasticity and restoration of inhibitory circuits after tSCS. Because chloride homeostasis is known to be disrupted after SCI, quantification of the membrane-bound potassium-chloride co-transporter KCC2 was performed to probe restoration of chloride homeostasis and explore its role in improvement of spasticity after tSCS. Our results indicate that tSCS initiated in the chronic phase of injury increases frequency dependent depression of the H-reflex and re-establishes membrane-bound KCC2. However, presynaptic inhibition of the H-reflex did not improve after tSCS in the chronic phase of injury. These findings suggest that 1) tSCS in the more clinically relevant chronic phase of SCI improves spasticity via upregulation of KCC2 and that 2) presynaptic inhibition does not mediate improvement in spasticity after tSCS in the chronic phase of injury.

**Disclosures:** **N. Yakas:** None. **D.C. Malloy:** None. **M. Cote:** None.

**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.06/V3

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** DOD Grant CDMRP, SCI 90008
NIH Grant T32 NS121768-01

**Title:** Tailoring Epidural Stimulation for the Treatment of Spasticity Following Spinal Cord Injury in Rodents

**Authors: *J. WEINBERGER**, D. C. MALLOY, M.-P. COTE;
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**Abstract:** Spasticity manifests in approximately 80% of spinal cord injury (SCI) patients. Pathological characteristics can involve a combination of involuntary muscle movements, co-contraction of antagonistic muscles, and hyperreflexia; all of which contribute to making daily activities challenging. Pharmacological intervention can aid in reducing these spastic symptoms; however, these treatments can have severe side effects such as seizures and dizziness, and depress overall spinal reflex excitability and muscle activity, further impeding motor recovery. Here, we examine epidural stimulation (ES) as an alternative strategy to decrease hyperreflexia following SCI. ES studies have historically centered on locomotor recovery, and the efficacy of ES has relied heavily on optimization in humans or the use of pharmacology in rodents. Little is known regarding if ES can serve as a form of treatment for spasticity following SCI and if it requires similar optimization. As a first step, we investigated the therapeutic potential of acutely administered individually tailored ES stimulation protocols after chronic SCI in rats featuring a severe contusion injury (250kdyn). A 15-channel epidural electrode array was positioned over hindlimb motoneuronal pools with close resemblance to electrodes used in SCI people to allow for individually optimized ES with the control of both anode and cathode positions. During a terminal experiment performed nine weeks post-injury, animals received a single ES treatment session (15 minutes, 40Hz, 0.8T) where specific anode and cathode positions were tested for each animal. The rate-dependent depression of the H-reflex was recorded from the plantar muscle in response to stimulation of the tibial nerve. Presynaptic inhibition was also probed via the effect of a stimulation to the posterior biceps-semitendinosus (PBSt) on the H-reflex. A significant increase in both the rate-dependent depression and presynaptic inhibition of the H-reflex was observed following optimized ES treatment. Our results suggest that tailored ES has the potential to decrease spasticity in SCI individuals without the use of pharmacological intervention.

**Disclosures: J. Weinberger:** None. **D.C. Malloy:** None. **M. Cote:** None.

**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.07/V4

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** Research reported in this publication was supported by the NINDS of the NIH under Award Number R01NS115877
Research reported in this publication was also supported by the Minnesota

SCI and TBI Research Program (2022 award contract: 214556; 2021 award contract: 191542)

**Title:** Comparison of lumbrosacral sensorimotor activity evoked by epidural, dorsal root, or transcutaneous stimulation within humans with spinal cord injury

**Authors: *A. J. ASP**[1,2], M. L. GILL[2], K. FERNANDEZ[3], D. D. VEITH[2], M. B. LINDE[2], C. J. MILLS[2], A. R. THORESON[2], K. D. ZHAO[2], P. J. GRAHN[2];
[2]Dept. of Physical Med. and Rehabil., [3]Mayo Clin. Grad. Sch. of Biomed. Sci., [1]Mayo Clin., Rochester, MN

**Abstract:** Over the last few years, several electrical stimulation modalities have emerged as potential therapies for restoring movement after spinal cord injury (SCI). Electromyogram (EMG) responses evoked from epidural stimulation (ES), dorsal root stimulation (DRS), or transcutaneous stimulation (TS) of the lumbosacral spinal cord may be used to guide selection of electrical stimulation parameters to improve motor function in persons with SCI. However, it is not known how evoked responses across spinal cord stimulation modalities differ within individuals. Here, we examine similarities and differences across ES-, DRS-, and TS-evoked responses in lower extremity muscles captured via skin surface EMG.At the time of this abstract submission, participants (n=8) underwent temporary implantation of percutaneous bilateral electrodes abutting the dorsal root ganglia and epidural regions. Symmetric, charge-balanced, biphasic pulses (pulse width: 250 μs; pulse frequency: 0.5 Hz) were delivered to DRS (0.5-6 mA) or ES (0.5-15 mA) electrodes as single or paired pulses spaced 15-400ms apart) while participants were in a relaxed, supine position. Prior to surgery, transcutaneous spinal cord stimulation (symmetric, charge-balanced, biphasic, 0.5 Hz, 5-100mA) was delivered to T10-L2 vertebral levels via skin surface electrodes, activating similar circuitries as ES and DRS. All stimulation modalities enabled lower-limb-evoked EMG responses. We observed significant differences in evoked EMG amplitude, latency, paired-pulse suppression, and muscle selectivity (left/right or proximal/distal) across the three stimulation modalities ($p<0.05$, Friedman Test with a Dunn's multiple comparisons posthoc test).These results demonstrate that ES, DRS and TS engage distal muscle targets through distinct mechanisms. In parallel to this work, we aim to leverage these data to build a patient-specific model of ES current distribution to aid in stimulation parameter selection for improving motor function after SCI.

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**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.08/V5

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** NIH SPARC OT2OD030537
NDSEG F-148887797

**Title:** Bladder reflexes evoked by sacral epidural spinal cord stimulation in computational models of the cat and human spinal cord

**Authors: *M. K. JANTZ**[1,2,6], X. FANG[2,3], A. DAMIANI[2,1], L. LIANG[2,1], C. GOPINATH[2,3], M. DEL BROCCO[2,1], F. LIU[3,2], U. AGBOR[2,3], T. NEWTON[7], E. NEUFELD[7], A. FASSE[7], K. T. HITCHENS[4], L. E. FISHER[2,3,1,6], E. PIRONDINI[2,3,1], M. CAPOGROSSO[5,1,2], R. A. GAUNT[2,1,3,6];
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**Abstract:** Lower urinary tract (LUT) dysfunction affects 94% of people living with spinal cord injury (SCI), and is consistently rated a top rehabilitation priority. One promising method to treat LUT dysfunction is epidural spinal cord stimulation (SCS), which we have used previously to activate LUT afferents, hypothesizing that this targeted neural recruitment would provide a mechanism to modulate LUT functions. However, it is challenging to experimentally evaluate the relative effects of the different nerves that contribute to LUT function and how the complex anatomy of the sacral cord affects SCS-driven activation. We explored this question in a highly realistic anatomical model of the sacral spinal cord.
First, we generated a 3D finite element model of the cat sacral spinal cord, using a high-resolution MRI scan of a postmortem cat spine, from the L5 vertebra to the sacrum. We used diffusion tensor imaging and tractography to generate morphologically realistic neural trajectories representing axons from the pelvic, pudendal, and sciatic nerves. We then performed finite element method simulations to compute the electromagnetic fields produced by electrodes spanning the sacral cord and cauda equina, and determined the recruitment threshold for each neural fiber in the model through electrophysiological modeling. Using these recruitment predictions as inputs to a network model of the pudendo-vesical bladder reflexes, we determined SCS-driven changes in bladder pressure. Finally, we repeated this process to generate a human sacral spinal cord model and predict neural recruitment under clinical conditions.
We found that the recruitment amplitudes of afferent and efferent neurons varied substantially between segmental levels; differences were high for the rostral segments, but no significant differences were found for the most caudal segments. These segmental differences were confirmed experimentally in anesthetized animals. This suggests that the unique anatomy of the sacral spinal cord region requires its own computational models, as models of the cervical, thoracic and lumbar spine typically predict exclusively afferent recruitment for clinically relevant stimulation amplitudes. Furthermore, we found that the LUT nerves are recruited across the full extent of the sacral cord and cauda equina, and that stimulation evokes frequency-dependent bladder contraction or continence reflexes throughout this region. Finally, in a human model, SCS also recruited LUT afferents, motivating further investigations of strategies to improve bladder function after SCI, and laying the groundwork for clinical studies using personalized SCS models.

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**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.09/V6

**Topic:** C.11. Spinal Cord Injury and Plasticity

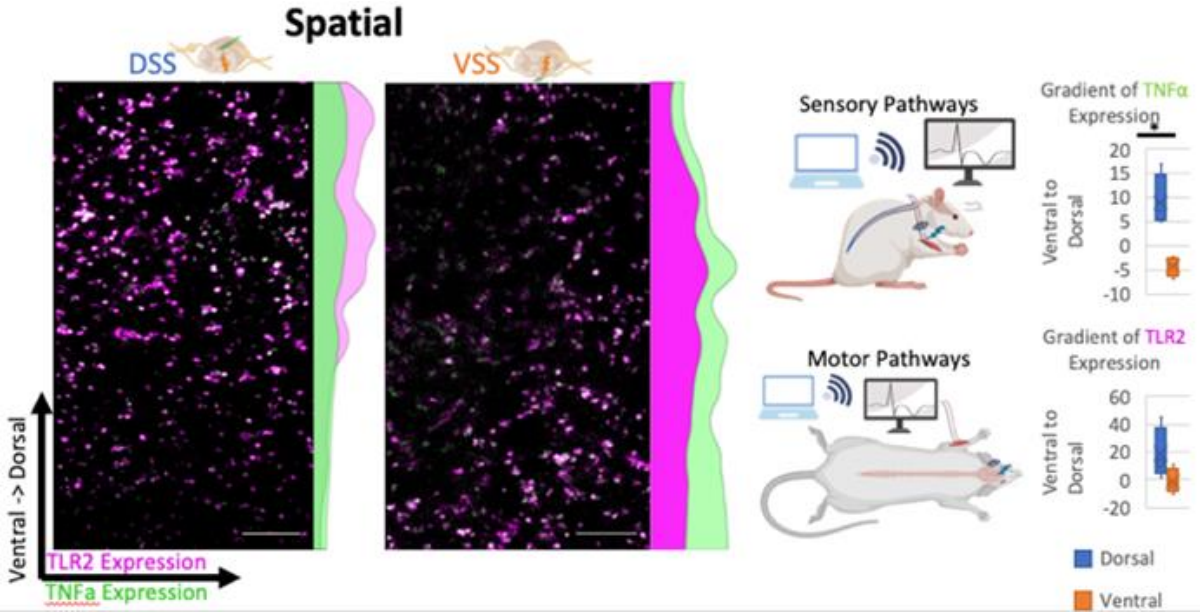
**Support:** Neilsen Fellowship 599274
Morton Cure Paralysis Fund
Wings for Life WFL-US-06/22
Walter Endowment

**Title:** Transcriptional Characteristics of Dorsal vs. Ventral Epidural Spinal Stimulation after Cervical Spinal Cord Injury in a Rat.

**Authors: *M. K. HOGAN**[1], J. MEJIA[2], A. M. FRAZIER[1], F. HUMES[1], G. W. BRITZ[3], P. J. HORNER[1];
[1]Neurosurg., Houston Methodist Res. Inst., Houston, TX; [2]Cornell University: Weill Cornell Med. Col., Houston, TX; [3]Neurosurg., The Methodist Hosp., Houston, TX

**Abstract: Introduction:** Various forms of electrical stimulation may improve outcomes following injury to the central nervous system. Still, mechanisms underlying benefit are not understood. We have developed a spinal stimulation system that can access ventral (VSS) and/or dorsal (DSS) aspects of the spinal cord. *We hypothesize that dorsal and ventral stimulation induce unique expression changes which can be independently leveraged to improve outcomes following SCI.* **Methods:** Rats were given a right sided injury using an OSU impactor. One week after injury, an electrode was placed at the C6 spinal level dorsally or ventrally. Animals were sacrificed and RNA was extracted or perfused for immunohistochemistry. **Results:** At one hour and one week of stimulation, dorsal and ventral stimulation produced unique changes in transcription with major transcriptional pathway differences. A gene ontology assessment indicated that transcriptional changes following acute dorsal and ventral stimulation (1 hour) were largely immune/inflammatory related, while at 1 week changes were associated with extracellular matrix remodeling and vascularization. We observed significantly more transcription of plasticity/regenerative associated genes with ventral stimulation after one week when compared with dorsal stimulation. RNAscope analysis after 1 week of stimulation revealed transcription gradients along the dorsoventral axis with ventral stimulation influencing ventral transcription more, whilst dorsal stimulation preferentially impacted transcripts in the dorsal spinal cord. **Discussion/Conclusion:** When ventral stimulation is compared with the effects of dorsal stimulation at the transcriptional level, we observed major differences in response to electrical stimulation. Transcriptional responses to stimulation location indicate location of spinal stimulation is a critical factor. Transcription gradients dependent upon the location of

stimulation as well as ontological shifts in affected pathways highlight that ventral and dorsal stimulation target unique cells and circuits.

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**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.10/V7

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** The work presented here was funded by Abbott Neuromodulation

**Title:** Electrode location variability in A-beta and off-target stimulating thresholds: Implications for human spinal lead migration

**Authors: *M. L. SETTELL**[1], A. DESHMUKH[4], K. P. CHENG[2], B. KNUDSEN[6], J. TREVATHAN[7], S. L. BLANZ[7], A. SKUBAL[8], N. VERMA[5], I. LAVROV[6], A. J. SUMINSKI[3], S. F. LEMPKA[9], A. SHOFFSTALL[10], M. ZHANG[11], K. LUDWIG[12];
[2]Biomed. Engin., [3]Univ. of Wisconsin-Madison, [1]Univ. of Wisconsin-Madison, Madison, WI; [5]Univ. of Wisconsin - Madison, [4]Univ. of Wisconsin, Madison, Madison, WI; [6]Mayo Clin., Mayo Clin., Rochester, MN; [7]Univ. of Wisconsin - Madison, Univ. of Wisconsin - Madison, Madison, WI; [8]UW-Madison, UW-Madison, Madison, WI; [9]Univ. of Michigan, Univ. of Michigan, Ann Arbor, MI; [10]Case Western Reserve Univ., Case Western Reserve Univ., Aurora,

OH; [11]Abbott Neuromodulation, Austin, TX; [12]Univ. of Wisconsin-Madison, Univ. of Wisconsin Madison, Madison, WI

**Abstract: Electrode location variability in A-beta and off-target stimulating thresholds: Implications for human spinal lead migration**

Introduction: Electrical stimulation of the spinal cord, using an implanted epidural electrode has been used to treat multiple chronic pain syndromes. Despite significant improvement in some subjects, the effects of lead migration are significant, as leads can migrate an average of 12 millimeters in human subjects[1]. This can result in lead revision surgery, and inherent additional risk. Movement of electrodes from a position of efficacy can result in decreased therapeutic effect, and off-target muscle activation. Measuring stimulation evoked epidural spinal responses (ESR) in the spine, has great potential in elucidating fundamental mechanisms, as well as providing an understanding of contact location to on and off-target thresholds.

Methods: In this study, clinical Octrode™ leads, were placed in the spinal canal of a swine model. We obtained biplane CT scans of the electrode positions post-implantation. Using ESRs, such as evoked compound action potentials (eCAPs) of the spine, and electromyography of off-target muscles, such as the intercostal and longissimus, we recorded activation thresholds and dose response curves.

Results: Our study demonstrated that changes in contact location, as little as 3 mm can result in changes to the threshold for activation of targeted a-betas, and off-target activation of surrounding muscles. This suggests that the movement of leads following implantation could significantly change the activation threshold in humans as well, limiting efficacy.

Conclusion: The location of stimulating contacts relative to the underlying anatomy during spinal cord stimulation (SCS) is important in understanding the mechanism and risk associated with SCS. As such, the postoperative period, when leads migrate, should be factored into the final lead position. Additionally, the results of our study suggest that using the eCAP components of ESR may indicate optimal locations to limit off-target affects and increase efficacy and should be optimized following the scarring-in period.

Acknowledgement: The work presented here was funded by Abbott Neuromodulation

**[1]**Dombovy-Johnson, Marissa L., et al. 2022. “Incidence and Risk Factors for Spinal Cord Stimulator Lead Migration With or Without Loss of Efficacy: A Retrospective Review of 91 Consecutive Thoracic Lead Implants.” *Neuromodulation: Journal of the International Neuromodulation Society* 25 (5): 731-37. https://doi.org/10.1111/ner.13487.

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**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.11/V8

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** NeuralCODR Fellowship at Houston Methodist Research Institute

**Title:** Therapeutic spinal cord stimulation post-injury triggers mitochondrial biogenesis through nr4a1

**Authors: *L. MONTIER**[1], M. HOGAN[1], L. SMITHERMAN[2], P. J. HORNER[1];
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**Abstract:** Objective: To determine the effect of therapeutic neurostimulation on mitochondrial biogenesis after spinal cord injury and explore the associated increase in neuronal Nr4a1.Rationale: We present the working hypothesis that therapeutic spinal cord stimulation induces mitochondrial biogenesis to promote neuronal regeneration after injury. Horner lab has demonstrated a cell-type specific upregulation of Nr4a1 in neurons 1 hour after stimulation. Nr4a1 is an early transcription factor with DNA-binding ability, and is exported from the nucleus at times of stress, such as stimulation.[1] In the cytosol, Nr4a1 can bind to bcl-2 and is transported to the mitochondria to induce fission.[2] This short-lived mitochondrial challenge induces mitochondrial biogenesis.Methods: We quantified Nr4a1 and TFAM, a mitochondrial transcription factor required for mitochondrial DNA replication, using immunohistochemistry in neurons (NeuN) after 8 weeks of daily ventral spinal cord stimulation at C6 following hemi-contusion-induced injury at C4 on the rat's dominant side. Control animals received the same injury, but a sham stimulation. Confocal images were collected from the dorsal and ventral horns, injured and uninjured sides of the spinal cord, with 3 tissue slices/animal and 3 random images from each ROI/slice. Images were blindly analysed to quantify total TFAM, total Nr4a1, and nuclear-localized Nr4a1 using the interpolation tool of ImageJ. Results: Preliminary results demonstrate that both Nr4a1 and TFAM are increased on both dorsal and ventral horns after stimulation (n=4 animals each group, >300 neurons per region; $p<0.05$). In addition to overall Nr4a1 increase, we also report an increase in both nuclear and cytosolic Nr4a1 ($p<0.01$).Conclusions: These results indicate that 8 weeks of neurostimulation increase mitochondrial biogenesis and likely improve ATP production as a mechanism that helps to promote neuronal survival through neurostimulation. Continuing work will examine mitochondrial dynamic and functional changes.
References1.Li H, Kolluri SK, Gu J, et al. Cytochrome c release and apoptosis induced by mitochondrial targeting of nuclear orphan receptor TR3. Science 2000;289:1159-1164.2.Lin B,

Kolluri SK, Lin F, et al. Conversion of Bcl-2 from protector to killer by interaction with nuclear orphan receptor Nur77/TR3. Cell 2004;116:527-540.

**Disclosures: L. Montier:** None. **M. Hogan:** None. **L. Smitherman:** None. **P.J. Horner:** None.

**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.12/V9

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** Natural Science and Engineering Research Council
Canada Foundation for Innovation
CIHR Postdoctoral Fellowship
CIHR Project Grant
Canada Research Chair in Functional Restoration
Alberta Innovates Postdoctoral Fellowship
Craig Neilsen Foundation Postdoctoral Fellowship
Neuroscience, Rehabilitation & Vision Strategic Clinical Network

**Title:** Combining an effective rehabilitative exercise paradigm with non-invasive forms of electrical stimulation after a motor complete spinal cord injury: A case study

**Authors: *D. J. MANN**[1,2,3], J. A. PORTER[1,2,3], D. O. OKUSANYA[1,2,3], Z. KARAMZADEH[1,2,3], S. ALLAHGHOLILOO[1,2,3], J. LEE[1,2,3], M. YUAN[1,2,3], M. ADIB[1,2,3], K. L. C. ELFSTEDT[1,2,3], T. S. BARSS[1,2,3,4], V. K. MUSHAHWAR[1,2,3,4];
[1]Univ. of Alberta, Edmonton, AB, Canada; [2]Dept. of Med., Div. of Physical Med. and Rehabilitation, Univ. of Alberta, Edmonton, AB, Canada; [3]Sensory Motor Adaptive Rehabil. Technol. (SMART) Network, Univ. of Alberta, Edmonton, AB, Canada; [4]Neurosci. and Mental Hlth. Institute, Univ. of Alberta, Edmonton, AB, Canada

**Abstract: Background/Objectives:** Functional electrical stimulation (FES)-assisted arm and leg (A&L) cycling is a rehabilitative exercise paradigm that is less labour intensive to administer, more cost-effective, and more generalizable to the community compared to body weight assisted overground walking interventions. Furthermore, FES-A&L cycling interventions have exhibited the ability to increase walking function after an individual has experienced an incomplete spinal cord injury (SCI) classified as ASIA Impairment Scale (AIS) C or D according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI). The goal of this study is to build upon this previous knowledge and examine whether the inclusion of non-invasive forms of transcutaneous spinal cord stimulation (tSCS) in conjunction with A&L could result in improvements for individuals living with a motor complete SCI.
**Methods:** This case study focused on a participant with an AIS B SCI classification. Cervical and lumbar tSCS were applied and combined with FES-assisted A&L cycling administered

1hr/day, 5 days/weeks. The participant completed 44 weeks of the 48-week training program. Periodical assessments included AIS, training load produced while cycling over time, and the time able to stand assisted with support from a walker and a physiotherapist to prevent the participant's knees from buckling.
**Results:** From pre-training to the most current assessment (44 weeks of training), there were no differences in the AIS scores. However, one key finding was that the total power output that was generated by the participant through tSCS paired FES-A&L cycling continuously improved over the sessions. Furthermore, the ability of the participant to stand supported with the aid of a physiotherapist and a walker increased to 33.5 s at 36 weeks of training from the initial 10s that occurred at pre-training. This ability to stand was further perpetuated when combined with tSCS, as at 36 weeks the participant could stand for 38.5 s.
**Conclusion:** This novel study demonstrates that combining FES-assisted A&L cycling with tSCS may be an effective exercise paradigm that can result in increased training load and assisted standing duration. Additional assessments will be included throughout the completion of this study to provide further improvements into the participants functional mobility and well-being. Finally, future studies will examine the benefits that arise from the coupling of epidural spinal cord stimulation with FES-assisted A&L cycling, in an individual who has experienced a motor complete SCI.

**Disclosures: D.J. Mann:** None. **J.A. Porter:** None. **D.O. Okusanya:** None. **Z. Karamzadeh:** None. **S. Allahgholiloo:** None. **J. Lee:** None. **M. Yuan:** None. **M. Adib:** None. **K.L.C. Elfstedt:** None. **T.S. Barss:** None. **V.K. Mushahwar:** None.

**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.13/V10

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** Canada Foundation for Innovation
Canadian Institutes of Health Research
Craig H. Nielsen Foundation
University of Alberta Hospital Foundation

**Title:** cFos expression after intraspinal microstimulation and epidural spinal cord stimulation: approach for immunohistochemical analysis

**Authors: *C. L. O'SULLIVAN**[1,2], N. TYREMAN[3], R. F. SHANTI[5], W. A. O'STEEN[5], S. MIRKIANI[2], M. BOAKYE[5], D. R. HOWLAND[5], V. K. MUSHAHWAR[4];
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Alberta, Edmonton, AB, Canada; [5]Kentucky Spinal Cord Injury Res. Center, Depts of Neurolog. Surgery, Univ. of Louisville, Louisville, KY

**Abstract: Introduction:** Spinal cord injury (SCI) presents many complications such as the inability to stand and walk. While an intervention to restore functional mobility does not yet exist, spinal cord neuromodulation has shown great promise. Two spinal cord stimulation (SCS) modalities are currently under investigation, epidural spinal cord stimulation (ESCS) and intraspinal microstimulation (ISMS), which pass electrical currents through electrodes targeting the lumbar enlargement. ESCS uses an array placed on the dura mater of the spinal cord with electrical fields indirectly activating the locomotor-related networks residing in the ventral horn. ISMS involves inserting ultrafine wires into the ventral horn, more directly targeting the locomotor networks. Due to the differences between the locations of stimulation provided by ESCS and ISMS, the mechanisms of action are likely different. To the best of our knowledge, this comparison has not been examined. The focus of this project was to develop a method to perform this comparison. **Methods:** In 4 female domestic pigs, 2 underwent 3 hours of ESCS. One of these pigs was anesthetized with sodium pentobarbital and the other with propofol. The remaining 2 pigs underwent 1.5 hours of unilateral hindlimb muscle stimulation, one under pentobarbital and the other under propofol anesthesia. Following the experimental protocol, the animals were euthanized, perfused, and the spinal cords were harvested for immunohistochemical (IHC) analysis. IHC analysis involved using a neuron-specific antibody and antibodies against cFos, a marker of neural activity, to determine where in the grey matter the cells bodies of active neurons resided. Comparisons were made between the pentobarbital and propofol anesthesia to determine which anesthetic regime was the most appropriate. **Results:** In both experimental conditions, propofol appeared to interrupt the expression of c-fos in spinal motor neurons. This was not the case with pentobarbital where positive, nuclear staining was seen. ESCS with pentobarbital demonstrated activation in the dorsal horn and intermediate region on the stimulated and unstimulated side of the cord but only ventral activation on the stimulated side of the cord. ESCS appeared to show a larger number of cFos expressing motor neurons than seen with direct hindlimb muscle stimulation. **Significance:** This research demonstrates that the type of anesthesia chosen during surgery is important for studying neural activation and provides a method for examining such in female domestic pigs. This will provide a protocol for future research examining the distribution and type of neural activation following ISMS and ESCS.

**Disclosures: C.L. O'Sullivan:** None. **N. Tyreman:** None. **R.F. Shanti:** None. **W.A. O'Steen:** None. **S. Mirkiani:** None. **M. Boakye:** None. **D.R. Howland:** None. **V.K. Mushahwar:** None.

**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.14/V12

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** United States Department of Defense
Canadian Foundation for Innovation
Canadian Institute of Health Research

**Title:** Evaluation of a Fully-implantable Intraspinal Microstimulation Implant Suitable for Humans in Domestic Pigs

**Authors: *S. MIRKIANI**[1,2,5], N. TYREMAN[3,5], D. WILSON[3,5], C. O'SULLIVAN[2,5], A. AREFADIB[2,5], P. TROYK[6,5], R. FOX[4,5], V. MUSHAHWAR[3,5];
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**Abstract: Introduction**: Intraspinal microstimulation (ISMS) is a novel technique that stimulates locomotor circuits in the ventral horn of the lumbar spinal cord using penetrating microelectrodes. ISMS has demonstrated promising results in restoring standing and walking after spinal cord injury in small animals (rats and cats). However, the long-term stability and functionality of ISMS implants in large mammals and humans remain a question. The larger size and higher range of motion of the spinal cord in humans could potentially lead to electrode dislodgement and failure of the implant. The objective of this study was to design, fabricate, and characterize a fully-implantable ISMS device suitable for humans, and test its functionality in a clinically relevant large animal model, which is the pig. **Methods:** The microelectrodes were fabricated from 50µm microwires (Pt-Ir, 80%-20%, insulated with polyimide) using femtosecond laser (1030nm, 343 nm) micromachining. The strain-relief system was developed using microcoils embedded in a silicone elastomer (OD:170µm) made from 25µm microelectrodes. The microcoils were joined to the microelectrodes using laser micro-welding (1070nm). An array of electrodes (16 electrodes) was fabricated and connected to a custom wirelessly controlled stimulator. The mechanical properties of the strain-relief system and joint breakage force (JBF) of the welded region were evaluated by the uniaxial tensile test. The electrochemical properties of the microelectrodes were tested. Moreover, the ISMS system was implanted and tested in 9 female domestic pigs to evaluate the isometric joint forces and kinematics of the evoked movements using ISMS. **Results and conclusion:** Fabricated microcoils were elastically stretched up to 30% of their initial length, which is more than the ~11% length change in the thoracolumbar region of the pig spinal cord. Laser peak power of 100W (Energy=100mJ, Pulse width=1ms) resulted in the highest JBF of 296.32mN, with failure of the samples occurring at the bare metal rather than at the weld region. This JBF was 10 times larger than the force causing electrode dislodgement. The impedances of electrodes measured at 1kHz were 3.2±0.2 KΩ and 20.5±2.0 KΩ in vitro and in vivo, respectively. The charge injection capacity of microelectrodes was 36 $\mu C.cm^{-2}.ph^{-1}$ and 16 $\mu C.cm^{-2}.ph^{-1}$ in vitro and in vivo, respectively. These values provide sufficient current amplitudes for the generation of functional movements in vivo. Angle changes in the hip, knee, and ankle joints evoked by ISMS generated a full range of motion. The results show the potential for future long-term use of these ISMS implants in humans.

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**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.15/V13

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** Natural Science and Engineering Research Council
Canada Foundation for Innovation
Canada Research Chair in Functional Restoration
Craig Neilsen Foundation Postdoctoral Fellowship
CIHR Postdoctoral fellowship
Alberta Innovates Postdoctoral Fellowship
CIHR Project Grant

**Title:** Mechanisms and tolerability of cervical transcutaneous spinal cord stimulation on modulation of lumbar limb activity

**Authors:** S. G. HEMAKUMARA[1,2], ***Z. KARAMZADEH**[3,2], D. J. MANN[4,2], M. ADIB[5,2], T. S. BARSS[4,2,6], V. K. MUSHAHWAR[2,4,6];
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**Abstract: Introduction:** Neuromodulation of spinal circuitry via non-invasive transcutaneous spinal cord stimulation (tSCS) is a potentially impactful approach for studying motor function and locomotion circuitry, and developing enhanced rehabilitation treatments after neurological impairment. The current study assessed the behavior of two tSCS stimulators as well as the effect of stimulation amplitude on the modulation of cervical-lumbar connectivity. The two stimulators were DS8R (Digitimer, Welwyn Garden City, UK) and NeoStim-5 (Cosyma Inc, St Petersburg, Russia).**Methods:** Adult, neurologically intact study participants (n=12; 6 female, 6 male) were recruited for the study. Two electrodes serving as the cathodes were placed on the C3-C4 and C6-C7 spinous processes of the neck, and two anodes were placed on the iliac crests. The stimulation threshold resulting in a spinally evoked potential in the biceps brachii muscle was determined. The amplitude for each stimulator was then slowly increased until reaching each participant's maximal tolerance level. The Hoffmann (H-) reflex and motor evoked potentials (MEPs) were used to assess the modulatory effects of cervical tSCS on the soleus and tibialis anterior (TA) muscles, respectively. H-reflexes and MEPs were obtained during tSCS stimulation at threshold and at maximal tolerance amplitudes for the two stimulators and compared to measures obtained without tSCS.**Results:** H-reflexes were obtained from 10 participants and MEPs from 9 participants. The maximum tolerated tSCS amplitude delivered by the DS8R stimulator (47.50 ± 12.66mA) was significantly lower than that delivered by the NeoStim-5 stimulator (60.90 ± 19.73 mA) ($p=0.0011$). Interestingly, there was no significant difference between H-reflex and MEP amplitudes evoked while applying tSCS using either stimulator nor during the application of tSCS at the threshold or maximal tolerable amplitude [H-reflex: $F(4,45)=0.083$, $p=0.9872$; MEP: $F(4,40)=0.3761$, $p=0.8243$]. **Conclusions:** In the current

study, there was a difference in sensation and tolerability of mainstream stimulators used in the field, with the NeoStim-5 having a more tolerable sensation on individuals. Unlike previous work, cervical tSCS did not facilitate or suppress the soleus H-reflex, nor did it influence TA MEPs. Moreover, stimulation intensity does not affect the amplitude of the H-reflex nor the MEP responses, in the soleus and TA, respectively. Delivering stimulation at the threshold intensity will have the same effect as delivering at maximum tolerable intensity.

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**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.16/V14

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** Natural Science and Engineering Research Council
Canada Foundation for Innovation
Canada Research Chairs

**Title:** Effect of Transcutaneous Spinal Cord Stimulation on Bimanual Arm Movements

**Authors:** B. PARHIZI[1], T. S. BARSS[2], ***V. K. MUSHAHWAR**[2];
[1]Neurosci. & Mental Hlth. Inst. and SMART Network, [2]Dept. of Med. and SMART Network, Univ. of Alberta, Edmonton, AB, Canada

**Abstract: Introduction:** Bimanual arm movements are a critical ability that facilitates the performance of numerous daily tasks. This ability is compromised after conditions such as spinal cord injury (SCI) or stroke. The overarching goal of this project is to develop an activity-based therapy that improves bimanual arm function after neural injury or disease. The focus of this study was on investigating the cortical substrates underlying bimanual arm movements and the modulatory effects transcutaneous spinal cord stimulation (tSCS) has on the performance of bimanual reaching movements and on modulating the associated cortical activity. **Methods:** Adult, neurologically-intact study participants sat in front of a bimanual KINARM exoskeleton and performed 3 visually-guided goal-directed reaching tasks: unimanual reaching, bimanual common-goal reaching in which both arms cooperatively reached to a common point in space, and bimanual dual-goal reaching in which each arm reached to a different point in space. Another group of participants performed the same movements with and without the application of cervical tSCS. Movement kinematics, electroencephalogram (EEG) spectral power density and interhemispheric connectivity (using coherence analysis) were assessed. **Results:** Dual-goal reaching movements had significantly larger movement time and movement error relative to unimanual and common-goal movements. Power in the EEG alpha band was significantly higher in the primary motor and sensory cortical regions during common-goal movements relative to

unimanual and dual-goal movements. Interhemispheric connectivity was also elevated in the common-goal task. During tSCS, movement time and error were significantly reduced in the common-goal movements. tSCS had no significant effect on these metrics in the unimanual and dual-goal movements. Spectral power density increased during tSCS in the sensorimotor cortices across all movements, especially in the beta band, while there was generally no effect of tSCS on interhemispheric connectivity. **Conclusion:** Goal-conceptualization is a critical factor in defining the behavioral outcome of bimanual movements. tSCS increased the synchronization of neural activity in sensorimotor regions, pointing a suppressive effect at the cortical level. Surprisingly, there was increase in interhemispheric connectivity with tSCS during the common-goal task even though kinematic performance was improved. Understanding the effects of tSCS on bimanual common-goal movements after neural injury or disease can pave the way for enhanced interventions that improve bimanual common-goal arm movements after these conditions.

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**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.17/V15

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** NIH Grant 5R01NS112535-05

**Title:** Augmenting epidural spinal cord stimulation with wide pulse neuromuscular electrical stimulation to tune lower limb movements and muscle activity

**Authors: *D. SONG**, M. C. TRESCH;
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**Abstract:** Epidural spinal cord stimulation (ESS) can produce or facilitate various functional lower limb movements such as stepping or standing after paralysis from spinal cord injury. However, due to natural anatomical variations in spinal roots and the broad distribution of charges from electrode contacts, it can be difficult to find appropriate stimulation parameters to produce task-relevant movements. For example, higher ESS amplitude risks producing coactivation of agonist and antagonist muscles and higher ESS frequencies might be susceptible to frequency dependent depression which reduces overall motor output. Targeting additional specific muscles with neuromuscular electrical stimulation (NMES) may help address these difficulties by fine tuning ESS evoked movements and muscle activation patterns. Additionally, “wide pulse” width NMES (1 ms) can recruit sensory proprioceptive afferents within the muscle, which project to various homonymous and/or heteronymous muscles. This could potentially provide a means to facilitate or inhibit muscles recruited by ESS enabling a broader range of control. To evaluate these possibilities, we measured electromyography (EMG) and kinematics in anesthetized rats in response to single ESS and NMES biphasic pulses. We performed

stimulation trials with various combinations of parameters such as amplitude and interstimulus pulse delay. NMES was delivered in ankle muscles using intramuscular electrodes. ESS was delivered using polyimide-based electrodes with 300-micron diameter gold contacts. We found that flexor EMG activity evoked by ESS is facilitated when ESS pulses are preceded by a medial gastrocnemius NMES pulse by 5-20 milliseconds (n = 10 rats). This facilitation was increased with increasing NMES intensity and disappeared with longer interstimulus pulse delays. To validate whether this facilitation is dependent on recruitment of sensory afferents and therefore spinal reflex circuitries, the dorsal roots were cut, and the stimulation paradigm was repeated (n = 3 rats). We observed that the facilitation was abolished after this cut, demonstrating that sensory afferents were indeed involved in this effect. We also observed some cases of inhibition and facilitation of proximal muscles at different NMES amplitudes and delays. These results suggest that augmenting ESS with NMES might be able to tune the flexion and extension movements evoked by ESS enabling new ways to improve lower limb movements during a rehabilitation protocol.

**Disclosures: D. Song:** None. **M.C. Tresch:** None.

**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.18/V16

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** International Spinal Research Trust grant NMN007

**Title:** The effects of cervical transcutaneous electrical stimulation and upper limb practice on manual dexterity and neural plasticity in people living with cervical spinal cord injury

**Authors: *A. CAPOZIO**, R. M. ICHIYAMA, S. L. ASTILL;
Univ. of Leeds, Leeds, United Kingdom

**Abstract:** Regaining upper-limb function is the main priority for rehabilitation for people living with cervical spinal cord injury (SCI) (Anderson, 2004). Task-specific training is currently the most effective intervention for upper-limb rehabilitation (Dietz and Fouad, 2014) and has been shown to promote recovery of upper-limb function when combined with transcutaneous electrical stimulation (TCES) of the spinal cord (Inanici et al., 2021). We compared the effects of 4 weeks (12 sessions) of task practice and 4 weeks of task practice combined with TCES on manual dexterity, brain plasticity and spinal plasticity in people living with cervical SCI.
Five participants (mean age = 48 ± 11, F = 5, injury from C3 to C7) volunteered: three participants underwent 4 weeks of upper-limb task practice (ULTP) followed by 4 weeks of ULTP paired with cervical TCES (ULTP+TCES) while two underwent 4 weeks of ULTP+TCES followed by 4 weeks of ULTP. Before and after the 4 weeks of ULTP and ULTP+TCES we assessed participants' manual dexterity via the Graded and Redefined Assessment of Strength,

Sensibility and Prehension (GRASSP). We ran a linear mixed-effects model to investigate the effects of Hand, Time and HandXTime interaction on the GRASSP scores. In two participants, we also measured brain excitability via motor-evoked potentials (MEPs) recorded using transcranial magnetic stimulation and spinal excitability (SEPs) via cervical stimulation of upper-limb muscles as participants underwent the two conditions.
The mixed-effects model revealed a non-significant HandXTime interaction ($F = 0.801$, $p = 0.608$), a significant effect of Time ($F = 46.742$, $p < 0.001$) and a non-significant effect of Hand ($F = 0.260$, $p = 0.624$). Pairwise comparisons between the baseline and post-interventions showed a non-significant increase in GRASSP scores after ULTP ($p = 0.086$), and a significant increase after ULTP+TCES ($p = 0.007$). Brain excitability increased by 60% after ULTP and remained constant after ULTP+TCES in P1; increased by 32% after ULTP+TCES and decreased by 42% after ULTP in P2. Spinal excitability decreased by 46% after ULTP and by 45% after ULTP+TCES in P1; decreased by 37% after ULTP+TCES and increased by 58% after ULTP in P2.
Our findings suggest that combining ULTP with TCES improves manual dexterity in people living with SCI more than ULTP alone. ULTP and ULTP +TCES had similar effects on neural plasticity, evidenced by increases in brain excitability and decreases in spinal excitability. Combining non-invasive spinal stimulation with task practice is a promising technique for promoting neural plasticity and improving manual dexterity in cervical SCI patients.

**Disclosures:** **A. Capozio:** None. **R.M. Ichiyama:** None. **S.L. Astill:** None.

**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.19/V17

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** TCMF-EP 110-02
MOST 111-2314-B-303-028

**Title:** Explore the mechanism of epidural electrical stimulation to improve lower limb motor function for patients with spinal cord injury using corticomuscular coherence.

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**Abstract:** **Motivation** Spinal cord injury (SCI) damages corticospinal motor circuitry and leads be paralysis. Epidural electrical stimulation (EES) has been demonstrated to recover voluntary control of lower limb motor function for patients with spinal cord injury. However, the mechanism of EES to improve the motor function of lower limbs was unclear. Corticomuscular

coherence is a common and beneficial method to study the mechanism of cerebral cortex's control of muscle activity. In this study, we used corticomusclar coherence to explore the mechanism of EES. **Methods** Three participants with cervical-level chronic SCI in AIS C, and the range of post-injury years was from 1 to 2 years, and the average age was 49.3 ± 19 years at the time of implant. They encountered rehabilitation with EES in rehabilitation sessions five times per week, and we collected corticomuscular coherence between electrocortical signals with electroencephalography (EEG) and lower limb with surface electromyography (sEMG) in pre-surgery and after-surgery for 15 weeks. Significant corticomuscular coherence was observed in the beta- (13-30 Hz) and gamma-range (31-60 Hz) for isotonic exercise. **Results and conclusion** We observed improvement in lower limb motor function and significant muscular EMG activity from three participants. Gamma-range corticomuscular coherence after-surgery for 15 weeks was more increased than pre-surgery. In the previous paper, Gamma-range corticomuscular coherence was observed in the healthy subject during isotonic exercise. Moreover, the muscular EMG activity of the lower limb and gamma-range corticomuscular coherence showed the same trend. Finally, the effectiveness of EES may be evaluated by gamma-range corticomuscular coherence.

**Disclosures: Y. Chen:** None. **S. Tsai:** None.

**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.20/V18

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** NIH NS104194
Craig Nielson Foundation
Philadelphia Foundation Brody Fund

**Title:** Epidural stimulation with viral BDNF therapy in combined bionic and biological SCI treatments improves recovery of function, delays onset of viral side effects, and maintains observed hindlimb muscle synergies and motor modularity

**Authors: *A. P. BORISYUK**, T. S. SMITH, K. J. DOUGHERTY, S. F. GISZTER;
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**Abstract:** Some interneuronal circuits in the spinal cord that synapse directly onto motor neurons may be organized for modular muscle control, i.e. as synergy groups, rather than individually. Electromyogram (EMG) recordings can detect the modular structures output by of these circuits and their inputs to motor pools as premotor drives, allowing inferences of modular spinal circuit changes after a spinal cord injury (SCI) and rehabilitation. Using dimensionality reduction techniques on hindlimb EMG, our lab has previously demonstrated modular spinal circuit structures in neonatal, adult, injured and uninjured rats. In the current study, we employed

these techniques to study changes in spinal circuits throughout rehab using combination therapies for SCI in rats. A combination of therapies may be most effective in improving function after a SCI. Although each therapy modality, i.e. rehab robotics training, biological (viral), and epidural stimulation (ES) improves function individually, we understand little about their synergistic interactions on function. We also have limited knowledge of the effects of combination therapies on muscle activation patterns and their underlying neuronal circuits, which may reflect different neuronal control strategies for motor coordination through recovery. Our lab has demonstrated enhanced locomotor outcomes in rats with complete thoracic 9/10 SCI after combining robot training with viral BDNF and ES. Prior work further revealed a potential critical period during the initial two weeks of training, where ES likely attenuates some spasticity development that can be an effect of the BDNF treatment on motor function. Spasticity can result in the eventual collapse of gained motor function in ~40% of rats. Broad-current spread ES centered at L2 and S1 prevented collapse over 6 weeks when combined with viral BDNF and robot training. In the current study, we tested if combined therapies with ES can prevent collapse beyond 6 weeks of rehab and if more selective ES can further improve stepping. We hypothesized that the combined treatment using localized ES would more selectively target the central pattern generators at L2 and S1, resulting in improvement in weight-supported stepping. We also hypothesized that modularity analysis of the hindlimb muscles will reveal patterns of spinal circuit reorganization and preservation of spatial synergy structure across the different rehab treatments and outcomes.

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**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.21/V19

**Topic:** C.11. Spinal Cord Injury and Plasticity

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Craig H. Neilsen Foundation Project #598563
Shriners Viral Core Grant #84051-PHI-21

**Title:** Chemogenetic afferent modulation in the rat contusion model of spinal cord injury to understand mechanisms of plasticity with locomotor training

**Authors: *G. T. KOMA**[1], K. M. KEEFE[2], G. MOUKARZEL[1], H. SOBOTKA-BRINER[1], J. CAPALDI[1], J. EISDORFER[4], B. RAUSCHER[5], T. J. CAMPION[3], J. CHEN[6], G. SMITH[1], A. SPENCE[1];

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**Abstract:** Spinal cord injuries result in life-long impairments that drastically reduce quality of life. With only 1% of spinal cord injury survivors making a full recovery, research into this field is essential. One method of treatment that has recently found promise is electrical epidural stimulation (EES). Unfortunately, electrical stimulation is not neuron-type specific and thus it is difficult to uncover exactly what pathways are contributing most to recovery, and how. Here we use the chemogenetic tool Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) to better enable circuit tracing, quantification of plasticity, and move towards selective activation of neuronal sub-types. We injected adeno-associated viral vectors (AAV2) containing an expression cassette for the excitatory DREADD (hM3Dq) bilaterally into the L3-L5 dorsal root ganglia (DRG). These DRG are thought to provide important feedback to the lumbar central pattern generator, and this excitation of afferents during treadmill training may be analogous to tonic EES. Kinematic data were gathered at 3, 5, 6, 7, 8 and 9 weeks post-injury using high-speed cameras. We used DeepLabCut (DLC) to extract 2D features from the two high speed video views, and then reconstructed the 3D coordinates with custom code. The study population contained two groups: contusion-DREADDs-CNO and contusion-mCherry-CNO animals. In this contused animal cohort, contusion-DREADDs-CNO animals displayed kinematics that were further from baseline during withdrawal of the DREADDs activator CNO (withdrawal of CNO was done in weeks 7 & 9 to determine its necessity). This suggested that plasticity in the spinal cord still relies on afferent activation to have observable behavioral outcomes. This is in contrast to a prior study in the hemisection model, where we found that withdrawal of CNO did not cause consistent changes in behavior. Based on our recent findings of afferent sprouting in the Clarke's columns and motor pools in the hemisection model that may underly these changes, we currently seek to trace the underlying changes in the contusion model for comparison.

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**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.22/V20

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** Wings for Life

**Title:** Vagus nerve stimulation paired with activities of daily living improve motor function in individuals with spinal cord injury.

**Authors: *K. MALLEY**[1], J. EPPERSON[2], B. STANISLAV[2], J. WRIGHT[2], E. ADEHUNOLUWA[2], D. PRUITT[3], C. SWANK[4], C. STEVENS[4], J. GILLESPIE[4], D. ARNOLD[4], J. WIGGINTON[2], R. L. RENNAKER[5], S. A. HAYS[6], M. P. KILGARD[7]; [1]Univ. of Texas at Dallas, RICHARDSON, TX; [2]Univ. of Texas at Dallas, Dallas, TX; [3]Univ. of Texas at Dallas, Richardson, TX; [4]Baylor Scott & White, Dallas, TX; [5]BBS, UT Dallas, Richardson, TX; [6]Bioengineering, Univ. of Texas At Dallas, Richardson, TX; [7]Behavioral and Brain Sci., Univ. of Texas, Dallas, Richardson, TX

**Abstract:** Spinal cord injury (SCI) commonly results in both sensory and motor dysfunction. Current rehabilitative strategies provide modest benefits, but these deficits persist in the majority of patients. Vagus nerve stimulation (VNS) is a promising treatment strategy that serves as an adjunct to traditional rehabilitative therapies to increase recovery after neurological injury. Preliminary data from an early feasibility study show that VNS paired with isolated upper limb movements appears to improve motor recovery after SCI. The degree of VNS-induced recovery is directly impacted by the therapy experience, and it is possible there would be more clinical benefit if VNS was paired with more complex upper limb movements as opposed to isolated movements. In this study, VNS was paired with performance of more complex activities of daily living (ADLs) was an effective method to treat functional deficits. A 33-year-old male with incomplete spinal cord injury (SCI) who was previously recruited in the ongoing early feasibility study (EFS) (NCT0428824) and was previously implanted with the ReStore VNS device received VNS paired with self-selected ADLs. The participant completed 36, 1-hour long sessions of VNS paired with rehabilitative training. Upper extremity function was assessed using the Graded Redefined Assessment of Strength, Sensation, and Prehension (GRASSP). ADL performance was assessed qualitatively by the time to complete each ADL and objectively by two therapists blinded to the experimental condition of the participant. Quantitative measures revealed a 16-point improvement in the participant's GRASSP score and a 63% reduction in task completion time. Initial data indicate that VNS paired with a functional, task-based paradigm is a promising approach to restore motor function after SCI.

**Disclosures: K. Malley:** None. **J. Epperson:** None. **B. Stanislav:** None. **J. Wright:** None. **E. Adehunoluwa:** None. **D. Pruitt:** None. **C. Swank:** None. **C. Stevens:** None. **J. Gillespie:** None. **D. Arnold:** None. **J. Wigginton:** None. **R.L. Rennaker:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Xnerve. **S.A. Hays:** None. **M.P. Kilgard:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MicroTransponder, Inc. F. Consulting Fees (e.g., advisory boards); MicroTransponder, Inc.

**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.23/V21

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** NINDS grant R01NS111234
NINDS grant R01NS111234-S1
NINDS grant R01NS111234-S2

**Title:** Dorso-ventral characterization of spontaneous activity and muti-modal sensory transmission in the chronically injured spinal cord in vivo

**Authors: *M. F. BANDRES**[1,2], J. L. GOMES[2], J. G. MCPHERSON[2,3,4,5];
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**Abstract:** Spinal cord injury (SCI) often leads to increased spontaneous activity (SpA) and responsiveness to nociceptive and non-nociceptive sensory feedback. This hyperexcitable state contributes to the development and maintenance of SCI-related neuropathic pain (SCI-NP). Generally, characterization of SpA and responsiveness to sensory feedback after SCI focuses on the dorsal horn, which is traditionally linked to sensory processing. SpA and sensory transmission after SCI are considerably less understood in the integrative intermediate gray and the motor-dominant ventral horn. Thus, it is unclear whether deep interneurons may contribute to clinical signs of sensory hyperexcitability (e.g., SCI-NP, spasticity, and spams). Here we characterize the firing dynamics of dorsal and ventral interneurons *in vivo* in neurologically intact rats and rats with chronic SCI *with* and *without* SCI-NP.
Experiments were approved by the IACUC of WUSTL and were conducted in adult, male Sprague-Dawley rats (17 intact rats; 14 rats with chronic T8 contusion, 7 with SCI-NP). Using microelectrode arrays spanning the dorso-ventral extent of the spinal gray matter at the L5 dorsal root entry zone, we characterized the firing dynamics of neurons during SpA and multi-modal sensory transmission (innocuous and noxious forces applied to the ipsilateral L5 dermatome). Primary outcomes included the number of spontaneously active neurons and neurons implicated in spinal pain processing (nociceptive specific [NS] and wide dynamic range [WDR] neurons) as well as spatiotemporal features of neural transmission during SpA and multi-modal sensory transmission throughout the gray matter (e.g., firing rate as function of anatomical region). Animals with SCI exhibited changes in deep interneuron firing dynamics consistent with a role in sensory hyperexcitability. For example, the mean firing rate of spontaneously active neurons in the intermediate gray (IG) of SCI-NP animals (12.52±1.00Hz) was higher than in neurologically intact animals (7.18±0.35Hz, p=0.0001). In addition, NS and WDR neurons were rarely found in the ventral horn of neurologically intact animals and those with SCI but no signs of SCI-NP, whereas ~34% of NS and ~14% of WDR neurons were identified in the ventral horn of animals with SCI-NP. The mean firing rate of these ventrally-located neurons during SpA and nociceptive transmission was indistinguishable from NS and WDR neurons in regions classically associated with spinal pain pathways. Together, our results suggest that ventral neurons may further exacerbate pathological sensory transmission after SCI.

**Disclosures: M.F. Bandres:** None. **J.L. Gomes:** None. **J.G. McPherson:** None.

**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.24/V22

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** NIH Grant R01NS111234
NIH Grant R01NS111234-S1
NIH Grant R01NS111234-S2

**Title:** Intraspinal microstimulation promotes simultaneous rebalancing of pathologic motor and nociceptive transmission in chronic spinal cord injury

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**Abstract:** Spinal cord injury (SCI) leads to debilitating physiological changes at and below the level of injury (e.g., reduced motor output, pelvic floor dysfunction and SCI-related neuropathic pain [SCI-NP]). Electrical spinal stimulation is a promising approach to treating these issues. Yet, spinal stimulation-based therapies for SCI are typically parametrized for motor rehabilitation alone; potential off-target effects are rarely assessed, and intentional multi-modal paradigms are lacking. Interestingly, the therapeutic benefits of motor-targeted spinal stimulation may rely, at least partially, on neural mechanisms that overlap with those presumed to underlie the ability of spinal stimulation paradigms to ameliorate signs of neuropathic pain stemming from non-SCI etiologies. Thus, here we explore whether motor-targeted spinal stimulation concurrently reduces spinal responses to nociceptive feedback.
We used spike train analyses to characterize the effects of motor-targeted intraspinal microstimulation (ISMS) on nociceptive transmission in 15 adult, male Sprague-Dawley rats with chronic SCI, including rats with and without behavioral signs of SCI-NP. Experiments were approved by the IACUC of Washington University. We conducted electrophysiological recordings &gt6 weeks after a T8 contusion using microelectrode arrays implanted at the L5 dorsal root entry zone. Sensory feedback was induced by mechanical stimulation of the ipsilateral L5 dermatome. ISMS was delivered to the spinal motor pools as a series of discrete pulses, 7Hz, ~90% motor threshold. Primary outcome measures centered about changes in the firing rate of nociceptive specific (NS) and wide dynamic range (WDR) neurons during induced nociceptive feedback during and after 30 min of ISMS.
We found that 30 min of motor-targeted ISMS resulted in net depression of spinal responsiveness to nociceptive sensory feedback. Specifically, ~60% of both NS and WDR neurons exhibited reduced firing rates during induced nociception after ISMS compared to pre-ISMS. WDR neurons also exhibited a progressive reduction in firing rate as ISMS duration increased, which remained depressed after ISMS was discontinued.
These results suggest that motor-targeted ISMS is capable of immediately modulating spinal nociceptive transmission, even in the chronically injured spinal cord. These actions appear to result in a net decrease in spinal responses to nociceptive sensory feedback, which would be

predicted to reduce behavioral signs of SCI-NP. They also suggest that it may be possible to develop an ISMS paradigm that affords multi-modal therapeutic benefits.

**Disclosures: M. Bandres:** None. **J.L. Gomes:** None. **J.G. McPherson:** None.

**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.25/V23

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** NIH Grant R01NS111234
NIH Grant R01NS111234-S1
NIH Grant R01NS111234-S2

**Title:** Intrinsic active membrane properties shape the firing dynamics of spontaneously active spinal interneurons in spinal cord injury-related neuropathic pain

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**Abstract:** Intrinsic active membrane properties are an essential component of motoneuron and wide dynamic range (WDR) neuron firing dynamics, modifying the input-output function of the cell to appropriately calibrate its responsiveness to the context in which it is recruited. After spinal cord injury (SCI), adaptive changes in the metabotropic receptors that govern active membrane properties often lead to supersensitivity and/or constitutive activity in neurons below the lesion. While these changes are intended to compensate for lesion-induced reductions in neuromodulatory drive, they often result in maladaptive sensorimotor consequences because they pathologically increase spinal responsiveness to sensory feedback. In motoneurons, this hyperexcitability contributes to debilitating spasms; in WDRs, SCI-related neuropathic pain (SCI-NP). Here, we asked whether active membrane properties also shape the firing dynamics of spontaneous neural transmission following SCI. Such a finding could offer insights into mechanisms contributing to the persistence of SCI-NP and the perception of pain in the absence of overt stimuli. All procedures were approved by the IACUC of WUSTL. We implanted microelectrode arrays *in vivo* into the lumbar enlargement of adult male Sprague-Dawley rats with chronic moderate to severe sensorimotor impairments following mid-thoracic contusion injury, including rats with SCI-NP. This approach enabled us to access single-unit spiking activity from a diverse population of interneurons spanning the dorso-ventral extent of the L5 spinal segment. It also enabled recording of both spontaneous neural transmission and evoked responses to varying modalities of sensory feedback, which were used to functionally classify neurons as WDR, nociceptive specific, etc. We show that spontaneous neural transmission is

indeed shaped by intrinsic active membrane properties, and across a wider extent of spinal interneurons than previously recognized. Specifically, we find the following discharge patterns in interneurons in the dorsal horn, intermediate gray, and ventral horn: (1) patterns consistent with the presence of robust persistent inward currents, including secondary (acceleration) and tertiary (stable) firing ranges as well as hysteresis with deceleration prior to de-recruitment; (2) self-sustained firing consistent plateau potentials; (3) switching between meta-stable functional states, such as endogenous bursting to plateau; and (4) spontaneous windup including *de novo* responsiveness to different modalities of sensory feedback. These exaggerated discharge patterns may reflect an endogenous spinal pain generator in SCI-NP.

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**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.26/V24

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** NIH Grant R01NS111234
NIH Grant R01NS111234-S1
NIH Grant R01NS111234-S2

**Title:** Sensory-targeted intraspinal microstimulation for spinal cord injury-related neuropathic pain

**Authors: *G. N. MORENO ROMERO**[1,2], M. BANDRES[1,2], J. MCPHERSON[1,2,3,4,5];
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**Abstract:** Spinal cord injury (SCI) results in debilitating sensorimotor impairments in regions innervated by spinal segments below the lesion. Among these is debilitating SCI-related neuropathic pain (SCI-NP). An integral component of SCI-NP is pathologically increased spinal responsiveness to both nociceptive and non-nociceptive sensory feedback. Interestingly, it has recently been found that intraspinal microstimulation (ISMS) intended to enhance voluntary motor output below a SCI simultaneously depresses spinal responsiveness to nociceptive feedback in neurons integral to SCI-NP. Here, we sought to determine whether an ISMS paradigm that specifically targets sensory-dominant regions of the spinal cord would be more efficacious at reducing spinal responsiveness to nociceptive feedback. All experiments were terminal, approved by the IACUC WUSTL, and conducted in 7 neurologically intact Sprague-Dawley rats. A laminectomy was performed at the T13-L2 vertebrae, and a dual shank microelectrode array was implanted into the gray matter of the L5 spinal segment. Single- and multi-unit neural transmission was recorded throughout the dorso-ventral extent of the gray

matter while mechanically probing the L5 dermatome to induce nociceptive or non-nociceptive cutaneous feedback before, during, and after sensory-targeted ISMS. ISMS was delivered in the deep dorsal horn as a series of discrete pulses, 7Hz, ~90% motor threshold. Outcome measures included the number and phenomenological type (i.e., wide dynamic range [WDR] or nociceptive specific [NS]) of neurons recorded during sensory transmission and spatiotemporal features of single and multi-unit discharge characteristics (e.g., firing rates). Surprisingly, sensory-targeted ISMS did not robustly modulate spinal responsiveness to sensory feedback. No changes in discharge characteristics were evident in response to either 2 or 10 min epochs of ISMS, and 30 min of sensory-targeted ISMS led only to a minor depressive effect in the mean firing rate of NS neurons. Multi-unit patterns of neural transmission were highly variable, with 1/4 rats exhibiting a net increase in responsiveness to sensory feedback, 1/4 exhibiting a decrease, and 2/4 being effectively invariant. These findings appear to suggest that motor-targeted, not sensory-targeted, ISMS is more efficacious at reducing spinal responsiveness to nociceptive feedback. However, it is unclear at present whether the apparent lack of effect is related to the ISMS parameters, which were chosen to mirror those used for motor-targeted ISMS, or if it is instead related to the neuromodulatory profile of motor-targeted ISMS.

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**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.27/V25

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** NIH NIDA RO1 DA047637
Louis and Harold Price Foundation
H & H Evergreen Foundation
J. Yang Family Foundation

**Title:** Dorsal and Ventral Cervical Epidural Electrical Stimulation Opposes Opioid-Induced Respiratory Depression via Different Respiratory Neural Circuits

**Authors: *J. PEYER**[1], R. HUANG[1], E. GARNER[2], Y. ZHOU[1], D. CHIOU[1], M. MADHAVAN[1], A. PATEL[1], M. YAMAMOTO[1], S. WANG[3], T. HOMSEY[2], T. LUO[2], H. VINTERS[2], N. SALAMON[4], M. NUWER[5], I. WU[6], J. C. LEITER[7], D. LU[1];
[1]UCLA Neurosurg., Los Angeles, CA; [2]UCLA Neurosci., Los Angeles, CA; [3]UCLA Intrnl. Med., Los Angeles, CA; [4]Radiology, David Geffen Sch. of Med. at UCLA, Los Angeles, CA; [5]UCLA Neurol., Los Angeles, CA; [6]UCLA Anaesthesiology, Los Angeles, CA; [7]Dartmouth Med. Sch., Lebanon, NH

**Abstract:** Opioids are a leading cause of overdose-related deaths in the US, accounting for 70.6% of fatalities in 2019 due primarily to respiratory depression. Epidural electrical

stimulation (EES) has emerged as a novel approach for facilitating rhythmic movement such as respiration in humans and rodent models. To reveal the mechanism underpinning modulation of respiratory neural circuits, we compared the effects of dorsal and ventral cervical epidural electrical stimulation (D-CEES, V-CEES) on respiration after opioid-induced respiratory suppression or depression (OIRD) via administration of remifentanil in anesthetized patients undergoing medically necessary spinal cord surgery. We hypothesized that V-CEES activates ventral horn motoneurons while D-CEES recruits local spinal circuits and tracts to supraspinal structures. We enrolled 43 patients receiving opioids during ventral (n = 25) and dorsal (n = 18) cervical spinal surgery. EES was delivered to the spinal cord (C2-C7) for <90 seconds at an optimal intensity (0.5-5mA) at 5Hz or 30Hz. The subjects' vital signs were recorded intraoperatively. Electromyograms (EMG) were used to monitor respiratory and upper extremity muscles such as the diaphragm, laryngeal, intercostal, genioglossal, and deltoid muscles bilaterally. The anesthesia stage was measured via electroencephalogram (EEG). A pneumotach recorded each patient's airway pressure. An independent anesthesiologist, tasked with ensuring patient safety, maintained a stable surgical plane of anesthesia via propofol in conjunction with minimal remifentanil prior to EES. We divided the responses into 2 states: ON- and OFF-State. The ON-State condition was defined as suppressed, but still present, respiration compared to baseline through an additional dose of remifentanil (0.001-.05mcg/kg/min). OFF-State condition was produced by dosing the subject with the lowest sufficient concentration of remifentanil (0.05-0.1mcg/kg/min) necessary to induce apnea. We observed four main differences between D- and V-CEES in regulating respiration in the presence of remifentanil: 1) D-CEES alone induced inspiratory phase resetting; 2) D-CEES induced longer lasting respiratory modulation after EES cessation; 3) D-CEES induced both frequency and tidal volume changes of respiration while V-CEES modulated the tidal volume more significantly; and 4) D-CEES respiratory modulation was inhibited more significantly during the OFF-state, while the most responsive spinal level to V-CEES, C6/7, maintained its respiratory modulation in both ON- and OFF-States. These observations suggest D- and V-CEES facilitate respiration via different neural circuits.

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**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.28/W1

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** Louis and Harold Price Foundation
H & H Evergreen Foundation
J. Yang Family Foundation

**Title:** Machine learning-enabled multiplex biomechanics quantification for trunk control deficits in human subjects with spinal cord injury

**Authors: *M. T. YAMAMOTO**[1], R. HUANG[1], Y. FREYVERT[1], P. A. TRUONG[2], M. MADHAVAN[1], G. S. YU[2], X. LIU[2], Y. ZHOU[1], N. J. WOBIG[2], M. A. BANTUGAN[2], A. GAJJAR[2], C. H. LIN[2], H. TAHA[2], J. C. LEITER[3], D. C. LU[1];
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**Abstract:** Trunk control plays a pivotal role in many essential activities such as controlling posture, facilitating voluntary limb movements, and improving gastrointestinal functions. Deficits of trunk control are prevalent in patients with spinal cord injury (SCI), compromising their life quality and limiting their capacity for independent living. However, interventions for improving trunk control in patients living with SCI remains under-studied. The lack of quantitative and standardized scales to measure trunk control in subjects with SCI is one of the main factors that limits therapy development. Due to the relative static nature in the kinematics of trunk control and the complexity of the coordination of muscles involved, the correlation between trunk control and the specific spinal level and injury severity has yet to be established. To understand how SCI impairs trunk stability, we established a random-forest-based (RF) regression model to perform multiplexed detection of biomechanics markers in order to identify SCI-specific alterations in the trunk control. Seven healthy control subjects and eighteen subjects with varying injury levels (high cervical to low thoracic) and severity (American Spinal Injury Association, ASIA, Impairment Scale A-D) of traumatic SCI were recruited to perform an array of seated trunk tasks. Three types of data were collected during the task: the success rate for completing the trunk task without the recruitment of additional body parts to aid in stabilizing the trunk, the three-dimensional (3D) kinematics features extracted from 18 motion capture markers placed bilaterally on the test subject, and the concurrent electromyography (EMG) data acquired bilaterally from four pairs of core muscles. The model was cross validated by two types of leave-one-out (leave one test or one patient out) with 67% accuracy. Our novel approach is promising and can be applied to predict the specific outcome in trunk function for SCI patients, thus allowing for individually tailored rehabilitation programs that target specific muscle groups responsible for motion impairments. By employing this machine learning-enabled multiplex biomechanics quantification, clinicians and researchers can gain valuable insights into trunk control deficits in SCI patients and advance rehabilitation strategies to enhance their functional outcomes.

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**Poster**

**PSTR022. Spinal Cord Injury: Neuromodulation Therapies I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR022.29/W2

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** Morton Cure Paralysis Foundation Grant
NIH Grant 5K12HD073945

**Title:** Optogenetic transduction of peripheral motor nerves after chronic spinal cord injury

**Authors: E. M. MORAVEC**[1], L. N. HERMANN[2], *J. J. WILLIAMS[3,2];
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**Abstract:** Optogenetic modulation of peripheral motor activity is an attractive tool for rehabilitating motor deficits in conditions such as spinal cord injury (SCI) as it possesses a number of potential benefits over electrical stimulation. In addition, prior studies using intramuscular virus injections for optogenetic labelling of peripheral motor nerves have suggested that these techniques may eventually be translatable to clinical use in humans. However, physiologic changes associated with SCI such as muscle atrophy, remodeling of neuromuscular junction (NMJ) structures and altered immune system activity may present challenges to the application of optogenetic techniques in a chronic SCI setting. In this study, we sought to determine the time window after SCI during which viral-mediated expression of optogenetic proteins in peripheral nerves is feasible, as well as compare timelines and levels of opsin expression in rat SCI models vs. non-injured rats. Fischer344 rats received a hemi-transection, contusion, or complete transection SCI at vertebral level T9 followed by a waiting period of two or four weeks. Next, rats received intramuscular virus injections in either the left or bilateral tibialis anterior muscles to target channelrhodopsin (ChR2) expression to the corresponding peroneal nerve(s). Weekly testing sessions were performed with each rat from two until twenty weeks after virus injection to evaluate functional opsin expression. For each session, transdermal optical stimulation sequences were applied to the target nerve while recording intramuscular electromyograms (EMG) from the injected muscle; force measurements were also made in a subset of rats. Nerve and muscle samples were examined for opsin expression and NMJ changes using immunohistochemistry at the conclusion of the experiment. Onset of optical sensitivity in targeted nerves was similar for all groups; rats began to produce EMG responses to optical stimulation between two and six weeks after virus injection. Optical stimulation also evoked foot movements in injured rats that could not voluntarily move their hindlimbs. Offset of optical sensitivity was variable across groups; rats stopped responding to optical stimulation as early as eight weeks after virus injection, though optical stimulation produced visible movements at twenty weeks after injection in many animals. Overall, these results demonstrate that optogenetic protein expression in peripheral motor axons via intramuscular virus injection is feasible following chronic SCI, offering further support for optogenetic stimulation as a potential rehabilitation therapy for restoring paralyzed movements.

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**Poster**

**PSTR023. Olfaction: Central Mechanisms and Behavior I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR023.01/W3

**Topic:** D.04. The Chemical Senses

**Support:** NIH U19 NS112953
NIH F31 DC020737

**Title:** Beyond coincidence: The role of respiration in olfactory cortical coding

**Authors: *R. M. BLAZING**[1], K. M. FRANKS[2];
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**Abstract:** A major goal of systems neuroscience is to understand how the brain represents sensory information. This is difficult to achieve in the olfactory system, as odor stimuli are complex and difficult to manipulate. Odors activate subsets of olfactory bulb (OB) glomeruli, which respond sequentially throughout the sniff cycle. The glomeruli project, via OB mitral and tufted cells, to the piriform cortex (PCx), where different odors activate distinct ensembles of neurons. Current models propose that the PCx functions as a coincidence detector, where individual neurons respond to specific combinations of co-activated glomeruli to form holistic "odor object" representations. However, there is little in-vivo evidence to support this combinatorial coding scheme. To understand how OB inputs are integrated in the PCx, we performed a series of experiments using patterned optogenetic stimulation of OB glomeruli while recording spiking in the PCx of the awake mouse. We first stimulated pairs of glomerulus-sized spots starting at inhalation onset, and varied the time interval between the spots, from 0-70ms. Surprisingly, synchronous stimulation rarely evoked supra-linear responses. Instead, neurons exhibited distinct temporal tuning curves that peaked at different inter-stimulus intervals. The shape of the two-spot tuning curves could often be predicted by summing the responses evoked by each spot in the pair. These results argue against a simple coincident input detector model.Instead, our results suggest that PCx neurons are tuned to the timing of their inputs relative to respiration. To test this hypothesis directly, we stimulated different spots distributed across the OB every 300ms, in pseudorandom order, and then binned each trial by its respiration phase. PCx neurons exhibited stimulation phase tuning, and the distribution of preferred phases of the population of neurons tiled the sniff cycle. Remarkably, a neuron's preferred phase was consistent across different stimulation sites. Blocking the ipsilateral nostril attenuated phase tuning, indicating that respiratory-modulated activity in the PCx has a peripheral origin. These results suggest that PCx neurons may receive similarly phase-tuned OB inputs. Our results indicate that individual PCx neurons are optimized to read out OB activity occurring during a particular window of the respiration cycle. This phase-to-rate coding scheme may allow for efficient representation of glomerular activity across the respiration cycle and demonstrates how temporal coding can facilitate information transmission across brain regions.

**Disclosures: R.M. Blazing:** None. **K.M. Franks:** None.

**Poster**

**PSTR023. Olfaction: Central Mechanisms and Behavior I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR023.02/W4

**Topic:** D.04. The Chemical Senses

**Support:** U19NS112953

**Title:** Neutral representational drift in the piriform cortex

**Authors:** F. PASHAKHANLOO[1], S. DASTE[3], S. SHUVAEV[1], A. FLEISCHMANN[3], ***A. KOULAKOV**[2];
[1]Cold Spring Harbor Lab., Cold Spring Harbor, NY; [2]Cold Spring Harbor Lab., Cold Spg Hbr, NY; [3]Neurosci., Brown Univ., Providence, RI

**Abstract:** Representational drift refers to over-time changes in neural activation accompanied by a stable task performance. Despite being observed in the brain and in artificial networks, the mechanisms of drift and its implications are not fully understood. We use chronic imaging of odor responses in the piriform cortex in combination with theory and simulations to develop and validate the model of this phenomenon. Here, we study the drift in a continual learning scenario, induced by the stochastic presentation of stimuli in a two-layer neural network. By decomposing the learning dynamics into the normal and tangent spaces of the minimum-loss neural manifold, we show the former correspond to a finite variance fluctuation, while the latter could be considered as an effective diffusion process on the manifold. Consistently with earlier experiments, we show that the drift rate is slower for a more frequently presented stimulus. Our model yields the prediction that drift should occur along the manifold of minimum loss, and, as such drift direction is restricted to the odor space which contains the representations of individual odorants. We collect data on chronic Ca imaging of odor responses in the piriform cortex. These data are used to test our theoretical predictions. Overall, our analysis yields a theoretical framework for better understanding of the drift phenomenon in biological and artificial neural networks.

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**Poster**

**PSTR023. Olfaction: Central Mechanisms and Behavior I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR023.03/W5

**Topic:** D.04. The Chemical Senses

**Support:** Grant-in-Aid for Scientific Research on Innovative Areas 21H05808 and 23H04335
JST-Mirai program JPMJMI19D1

**Title:** Neural odor representation at early latency determines behavioral odor discrimination performance

**Authors: *M. KATO**[1], T. OKUMURA[2], K. TOUHARA[1], M. OKAMOTO[1];
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**Abstract:** To understand the sense of smell, it is crucial to investigate the relationships among odor chemical structures, neural activities, and behavioral responses. The relation between odor chemical properties and neural activities has mainly been investigated using animal models. Those studies have suggested that the encoding of chemical information in the brain undergoes a gradual reshaping process, leading to the neural foundations of perception. However, knowledge regarding the human olfactory system is limited. To date, only a few fMRI studies have reported that odor chemical and perceptual information is represented at distinct regions of the olfactory cortex. Due to the low temporal resolution of fMRI, the dynamic changes in chemical representation over time in the human brain remain unclear. Moreover, even in rodents, it remains uncertain whether the initial chemical representation serves any purpose beyond a precursor to the formation of perceptual representations. Thus, in this study, we conducted two types of EEG experiments to examine the temporal dynamics and functional significance of odor representations. In Experiment 1, we recorded EEG responses to structurally and perceptually diverse odors. Using time- and frequency-resolved representational similarity analysis, we investigated the relationships between the chemical properties of odors, their perceptual properties, and neural activities. We also assessed the inter-subject correlation between the degree of chemical representation in the brain and odor discrimination ability to understand the functional role of these neural representations. In Experiment 2, we recorded EEG responses while participants performed an odor discrimination task and analyzed the differences in odor decoding accuracy between correctly and incorrectly answered trials. Our findings revealed that neural representations of odor chemical information emerged prior to perceptual representations, particularly in the theta and delta frequency bands. In the early theta band, the degree of chemical representation exhibited a positive correlation with odor discrimination ability, and the accuracy of odor decoding was higher in trials where subjects correctly answered the odor discrimination task. These results provide insights into the spectro-temporal dynamics of odor representation in the human brain and suggest that, during early latency, the neural representation of chemical information serves as a foundation for odor discrimination performance at the behavioral level.

**Disclosures:** **M. Kato:** None. **T. Okumura:** None. **K. Touhara:** None. **M. Okamoto:** None.

**Poster**

**PSTR023. Olfaction: Central Mechanisms and Behavior I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR023.04/W6

**Topic:** D.04. The Chemical Senses

**Support:** NIDCD (R21DC019193 to JPB and R01DC006213 to MM)

**Title:** Role of the anterior olfactory nucleus to nucleus of lateral olfactory tract pathway in odor-guided behaviors

**Authors: *J. P. BHATTARAI**, Y. WANG, W. LUO, M. MA;
Dept. Of Neurosci., Univ. of Pennsylvania, Philadelphia, PA

**Abstract:** The olfactory bulb projects to multiple olfactory cortical areas including the anterior olfactory nucleus and tenia tecta (AON for simplicity), which then connects to the downstream structures that are crucial for odor-guided behaviors. The anatomical connections and functions of the AON to its downstream targets are not well established. To gain genetic access to the AON neurons, we performed a differential gene expression search in the Allen Brain Atlas and identified the neuromedin B receptor (NMBR) gene as a molecular marker for the AON neurons. Using the CRISPR-Cas9 gene-editing approach, we generated an NMBR-Cre knock-in mouse line. Anatomical tracing from the AON neurons revealed specific reciprocal connections with the nucleus of lateral olfactory tract (NLOT) of the cortical pallial amygdala. Whole-cell patch clamp recordings combined with optogenetic activation confirmed that AON neurons make monosynaptic connections onto NLOT neurons. Furthermore, in vivo fiber photometry revealed odor and/or sniff induced $Ca^{2+}$ signals in the AON neuron axonal terminals in the NLOT as well as in NLOT neurons (specifically targeted in the SLA-Cre mouse line) of freely behaving mice. Finally, ablation of excitatory neurons in the NLOT not only impaired olfactory guided food search and social discrimination but also disrupted aversive behavior to a synthetic predator odor. Consistently, chemogenic inhibition of NLOT projecting AON neurons also disrupted olfactory guided behaviors. Taken together, these results indicate that the NLOT and AON-NLOT pathway play a critical role in a variety of odor-guided behaviors.

**Disclosures: J.P. Bhattarai:** None. **Y. Wang:** None. **W. Luo:** None. **M. Ma:** None.

**Poster**

**PSTR023. Olfaction: Central Mechanisms and Behavior I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR023.05/W7

**Topic:** D.04. The Chemical Senses

**Title:** Circuits for odor discrimination and odor generalization in the mouse piriform cortex.

**Authors: *F. SANTOS-VALENCIA**[1], K. M. FRANKS[2];
[2]Neurobio., [1]Duke Univ., Durham, NC

**Abstract:** Animals must learn to both discriminate between and generalize across different odors to survive. For example, a mouse foraging for food must learn to discriminate the odor of a rotten fruit from a fresh fruit. At the same time, the mouse must be able to generalize across different types of fruit odors. Where and how these two processes are implemented remains unclear. The piriform cortex (PCx) is only two synapses away from the olfactory epithelium and is the first and largest region in the olfactory pathway. The PCx contains two types of projection neurons, pyramidal cells (PYRs) and semilunar cells (SLs). PYRs form an extensive recurrent intracortical network while SLs do not receive recurrent input. In addition, both cell types project to different regions making them suitable candidates to implement different computations during olfactory learning. We have optotagged hundreds of SLs and PYRs and recorded their spiking in head-fixed mice performing odor discrimination in a two alternative forced choice task, and have found that cell-specific odor representations emerged after odor learning. Mice were initially trained to discriminate between two distinct odorants. After becoming proficient, mice were presented with the two odorants and mixtures of the two at varying ratios. SLs and PYRs spiking activity was recorded during the first session (S1) after introducing the mixtures and the last session (S2) when mice were fully proficient at the task. We found that both cell-type responses to the odorants and mixtures were decorrelated during S1. Interestingly, by S2 responses to the odorant mixtures clustered with the dominant mixture component, which matched the mouse's behavior. This suggests that both cell types can support discrimination and generalization depending on the learning stage. However, when training a classifier to explicitly generalize across mixtures with the same dominant component, the ability of SLs to generalize did not change across sessions but the ability of PYRs changed dramatically. PYRs performance was at chance levels during S1 and almost perfect during S2, outperforming SLs. This suggests that PYRs responses are highly plastic and adapt better to the behavioral demands. Our data indicate that odor discrimination and generalization are implemented in PCx, and suggest that distinct cell types - with distinct downstream projections - perform subtle but distinct computations to transform sensory input to ultimately drive appropriate behaviors. In general, our findings shed light on the role of segregated cortical circuits and provide insight into how their specific computations might be linked to behavior.

**Disclosures: F. Santos-Valencia:** None. **K.M. Franks:** None.

**Poster**

**PSTR023. Olfaction: Central Mechanisms and Behavior I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR023.06/W8

**Topic:** D.04. The Chemical Senses

**Support:** NIH DC019124 to Linster, Cleland and Smith

**Title:** Modulation of oscillations in the anterior olfactory nucleus and ventral hippocampus in context driven odor discrimination task.

**Authors: *D. E. SCOTT**[1], *D. SCOTT[2], O. D. ESCANILLA[1], M. EINHORN[1], D. M. SMITH[1], T. A. CLELAND[1], C. LINSTER[3];
[1]Pyschology, [3]Neurobio. and Behavior, [2]Cornell Univ., Ithaca, NY

**Abstract:** The anterior olfactory nucleus (AON) is a secondary olfactory network receiving afferent input from the olfactory bulb and efferent input from the ventral hippocampus (vHC), among other areas. We and others have shown that connections from the vHC to the AON are important in associating odors with physical context. For example, both the vHC and AON are required to solve a context-modulated olfactory discrimination task, whereas when textures rather than odors are used as the primary stimulus, the vHC is still required but the AON is not. We hypothesize that coordinated neural activity between these areas is more coherent and organized during this contextually modulated odor discrimination task, in which required contextual information is transferred from the vHC to the AON, compared to similar odor discrimination tasks in which the physical context is irrelevant. We here record simultaneous local field potentials in the AON and vHC of awake/behaving rats performing either a simple or a context-modulated odor discrimination task. We hypothesize that interareal LFP dynamics will be more strongly coherent and directional when vHC input to the AON is needed to solve a task than when it is not.

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**Poster**

**PSTR023. Olfaction: Central Mechanisms and Behavior I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR023.07/W9

**Topic:** D.04. The Chemical Senses

**Support:** ERC

**Title:** Novelty detection and efficient coding in the zebrafish homolog of piriform cortex

**Authors: *T. CAUDULLO**, R. W. FRIEDRICH;
Friedrich Miescher Inst. for Biomed. Res., Basel, Switzerland

**Abstract:** Area Dp of the teleost forebrain is the main synaptic target of the olfactory bulb and homologous to piriform cortex. Its structure and function suggest that it might store odor memories. Consistent with this hypothesis, we found that bilateral lesions of Dp in adult zebrafish impaired memory recall in an olfactory discrimination task. To explore Dp function in vivo, we measured odor-evoked calcium signals in the ventral portion of posterior Dp (vpDp) using 2-photon imaging through a microprism in awake head-fixed fish. Neurons in vpDp respond to stimulation with distributed and dynamical activity patterns. Responses were attenuated in an odor-specific manner after the first application of a novel odor. During subsequent trials, neuronal population activity underwent further changes that resulted in a

sparsening and gradual stabilization of odor-evoked neuronal population activity. Although population responses exhibited considerable trial-to-trial variability they allowed for decoding of odor identity by a simple linear classifier. As mean activity decreased over trials, linear decoding accuracy remained stable or even improved. Hence, information about odor identity became represented more efficiently by fewer action potentials. Together, these observations suggest that Dp represents both the identity and the novelty of odors by at least partially separable components of population activity patterns. Consistent with this hypothesis, we discovered that neural dynamics is confined to odor-specific nonlinear manifolds in state space, separating responses according to identity and novelty. Taken together, our results indicate that novelty is an attribute of olfactory stimuli that is strongly represented in Dp. As novelty detection requires the comparison of sensory input against memory, this observation supports the notion that Dp (and piriform cortex) perform memory-based classification of odor representations. Moreover, our results indicate that young memories become increasingly efficient while remaining informative about odor identity, which is consistent with computational models of memory that have recently received attention. We are currently investigating how odor-reward associations modify representations of specific odors in Dp.

**Disclosures:** **T. Caudullo:** None. **R.W. Friedrich:** None.

**Poster**

**PSTR023. Olfaction: Central Mechanisms and Behavior I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR023.08/W10

**Topic:** D.04. The Chemical Senses

**Title:** The ventral tegmental area and hypothalamus as possible structures involved in the olfactory pathway between the olfactory bulb and cerebellum

**Authors: *J. TORRES**, P. CARRILLO-CASTILLA, J. MANZO, G. A. CORIA-AVILA, M. E. HERNÁNDEZ, J. FISHER, C. A. PÉREZ, L. I. GARCÍA;
Univ. Veracruzana, Xalapa, Mexico

**Abstract:** The cerebellum has been associated with voluntary and spontaneous movement planning functions, maintenance of balance and posture, cognition, memory, vestibular function, and recent studies have also established the involvement of the cerebellum in the olfactory system. However, the specific pathway through which olfactory information reaches the cerebellum remains unknown. One potential communication route involves the Ventral Tegmental Area (VTA) and the hypothalamus, connected to the primary olfactory cortex and the cerebellum. This study aims to investigate the potential role of the VTA and the posterior lateral hypothalamic area as mediators of olfactory information transmission between the olfactory bulb and the cerebellum. To conduct the research, 24 male Wistar rats were utilized. Unipolar electrodes were surgically implanted in three target areas: the olfactory bulb, Crus I of the cerebellum, and the VTA or the posterior lateral hypothalamic area. Following recovery,

multiunit activity (MUA) recordings were obtained while stimulating the rats with three distinct odorants: (1) almond scent to activate the primary olfactory system, (2) woodshaving from cages of sexually receptive females to stimulate the accessory olfactory system, and (3) clean woodshaving as a control stimulus. Preliminary results indicate MUA signal amplitude and frequency changes at the recording sites during stimulation with different odorants. Furthermore, temporal changes in MUA between the recording sites were analyzed to explore the pathway of olfactory information transmission from the olfactory bulb to the cerebellum via the VTA or the posterior lateral hypothalamic area.

**Disclosures:** **J. Torres:** None. **P. Carrillo-Castilla:** None. **J. Manzo:** None. **G.A. Coria-Avila:** None. **M.E. Hernández:** None. **J. Fisher:** None. **C.A. Pérez:** None. **L.I. García:** None.

**Poster**

**PSTR023. Olfaction: Central Mechanisms and Behavior I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR023.09/W11

**Topic:** D.04. The Chemical Senses

**Support:** NIH R01 DC014701

**Title:** Spike timing-based odor representation in the olfactory system

**Authors: *T. A. CLELAND**, J. C. WERTH, M. G. MARISCAL, M. EINHORN; Psychology, Cornell Univ., Ithaca, NY

**Abstract:** In the mammalian olfactory bulb (OB), gamma oscillations in the local field potential are generated endogenously during odor sampling, and slower beta oscillations arise when the OB couples dynamically with piriform cortex (PCx). Such oscillations arise from dynamical systems that generate organized periodic behavior in neural circuits, and correspond to spike timing constraints at millisecond timescales. As spike timing control on these timescales has clear implications for synaptic integration efficacy and spike timing-dependent plasticity, we explored the capacity of timing control on this scale to encode odorant information. First, we used OB slices to examine the spike timing dynamics evoked by “fictive odorants” generated via the spatiotemporally patterned optogenetic stimulation of olfactory sensory neuron axonal arbors. We found that a small proportion of principal neurons phase-locked strongly to the fast oscillations evoked by fictive odorants, and exhibited tightly coupled spike-spike synchrony on the gamma timescale during this stimulation. Moreover, the specific population of synchronized neurons differed based on the “quality”, but not the “concentration”, of the fictive odorant presented, and was conserved across multiple presentations of the same fictive odorant. Second, we analyzed the coordination of OB and PCx spike timing in vivo, using a public dataset of simultaneous electrophysiological recordings from both structures (pcx-1, NSF CRCNS.org, contributed by Bolding & Franks). Odor stimulation evoked characteristic epochs of gamma and beta oscillations, which became coherent during the beta epoch. Ensembles of principal neurons

in OB and PCx phase-locked to these evoked gamma and beta oscillations, and synchronized with one another in odor-specific patterns. Interestingly, we found that neural representations based on principal neuron synchronization patterns exhibited different properties than the traditional metric predicated on spike rates. For example, in OB slices, representations based on synchrony discarded nearly all concentration-based variance, whereas spike rates still incorporated concentration information. Second, in vivo, following odor onset, both the OB and PCx demonstrated rapid increases in both the mean firing rate and spike synchronization of principal neurons; however, whereas firing rates in PCx rapidly dropped back to baseline, the elevated spike-spike synchronization levels persisted for the duration of the odor stimulus. Spike synchronization patterns are likely to underlie superior metrics for understanding neural computation and interareal communication.

**Disclosures: T.A. Cleland:** None. **J.C. Werth:** None. **M.G. Mariscal:** None. **M. Einhorn:** None.

**Poster**

**PSTR023. Olfaction: Central Mechanisms and Behavior I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR023.10/W12

**Topic:** D.04. The Chemical Senses

**Support:** NIDCD Grant R01DC019405-01A1
NSF GRFP

**Title:** Robustness to noise in the olfactory system: behavioral and neural mechanisms

**Authors: *S. LYONS**, P. A. ALICEA-ROMÁN, J. A. GOTTFRIED;
Neurol., Univ. of Pennsylvania, Philadelphia, PA

**Abstract:** The natural odors we encounter every day are complex, volatile mixtures that shift dynamically through space and time, face interference from other stimuli, and appear across a wide variety of contexts. The noise that arises from these common sources of spatiotemporal and contextual variability poses a significant challenge to the olfactory system. However, we know very little about how the olfactory system manages such noise to support robust odor identification and learning. We hypothesize that olfactory noise is processed in a manner consistent with approximate Bayesian inference. Whereas precise information is amplified and used to update beliefs about odor identity, noisy information is suppressed. By suppressing noisy information and amplifying precise information, the olfactory system can then make reliable perceptual judgments. Neurobiologically, we hypothesize that neuromodulatory systems mediate this process by amplifying the gain of neural populations carrying precise olfactory information and dampening the gain of neural populations carrying noisy olfactory information. To test these behavioral and neural hypotheses, we developed a probabilistic olfactory learning paradigm under 7T fMRI in which participants identified the dominant odor in mixtures of β-pinene (pine)

and isoamyl acetate (banana). We manipulated the noise of the dominant odor by varying the ratios of the odor mixtures along a continuum from 100% pine to 100% banana. Consistent with our hypothesis, participants encoded information about the noisiness of the dominant odor and used this information to proportionately update their beliefs about its identity. Moreover, our neural data preliminarily support the role of neuromodulatory centers in the basal forebrain and brainstem in weighting the noise of olfactory information, as evidenced by measures of functional connectivity with piriform cortex. Overall, these results are consistent with our hypothesis that the olfactory system amplifies precise information and suppresses noisy information in the service of robust odor identification and learning. Furthermore, these results suggest a more general Bayesian processing scheme in the olfactory system that should be investigated in future research.

**Disclosures: S. Lyons:** None. **P.A. Alicea-Román:** None. **J.A. Gottfried:** None.

**Poster**

**PSTR023. Olfaction: Central Mechanisms and Behavior I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR023.11/W13

**Topic:** D.04. The Chemical Senses

**Title:** Early Life Adversity has different, sex-dependent impacts on odor perception and its underlying neural mechanisms in mice

**Authors: *A. ATHANASSI**[1], L. CHALENÇON[2], L. FOUCAULT[3], O. RAINETEAU[3], A. FRANCOIS[4], E. BOURRINET[4], K. BATH[5], N. MANDAIRON[1];
[1]CNRS UMR 5292 INSERM 1028, Lyon Neurosci. Res. Ctr., Bron, France; [2]Dept. of Psychiatry, Weill Cornell Med. Col., New York City, NY; [3]Univ. Lyon U1208, Stem Cell and Brain Res. Inst., Bron, France; [4]CNRS UMR5203, Inst. de Génomique Fonctionnelle, Montpellier, France; [5]Dept. of Psychiatry, Columbia Univ. Med. Col., New York City, NY

**Abstract:** Early Life Adversity (ELA) significantly increases the later risk for depression with sex disparities in humans. Depression has been associated with disturbances in the hedonic perception of odorants. Olfaction serves a primary role in social interactions, food intake, and hedonic responding to daily pleasures. Thus, the study of altered olfactory perception and hedonic processing of chemosensory cues after ELA may provide insights into basic neurobiological disturbance underlying pathology. Further, such studies may identify key pathways that impact quality of life, contributing to the development and severity of depressive symptoms as well as sex differences in risk. Here, we used the limited bedding and nesting protocol in mice to model ELA in the form of fragmented maternal care. The aim of this study was to determine whether ELA altered the hedonic processing of odorants in adult male and female mice, and to identify neural substrates underlying those effects. First, we found that male and female pups showed delays in somatic growth around the time of ELA but that females quickly compensate for this loss during the peri-adolescent period, an effect that was not as

robust in males. Finally, we found evidence of depressive-like outcomes and altered perception of pleasant odorants in adult male but not female mice with history of ELA. We used fine structural analysis of neurons, cellular imaging and fiber-photometry to decipher the neural bases of ELA. We found sex-selective effects on the morphology and activity of the neurons in the olfactory bulb of ELA reared mice in response specifically to pleasant odorants. Additionally, in adult males only, we found altered recruitment of the reward system with changes in the functionning of the olfactory tubercle and ventral tegmental area, key structures involved in the odor hedonic coding. These results highlight potential impacts of ELA on network development and response to exogenous signals, diminishing interest in pleasant odorants with sex specificity. The current results point to ELA altering the neural substrates involved in olfactory sensory function and reward in males, with implications for understanding sensitivity or resilience for anhedonia and symptom severity in individuals at risk for depression associated with prior history of ELA.

**Disclosures:** **A. Athanassi:** None. **L. Chalençon:** None. **L. Foucault:** None. **O. Raineteau:** None. **A. Francois:** None. **E. Bourrinet:** None. **K. Bath:** None. **N. Mandairon:** None.

**Poster**

**PSTR023. Olfaction: Central Mechanisms and Behavior I**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR023.12/W14

**Topic:** D.04. The Chemical Senses

**Support:** NSF CAREER to DS
MSU Startup to DS

**Title:** Detecting lung cancer using honeybee olfactory neural circuits

**Authors:** ***M. PARNAS**[1], E. COX[1], S. W. SANCHEZ[2], A. FARNUM[2], N. LEFEVRE[1], S. MILLER[1], D. SAHA[2];
[2]Biomed. Engin., [1]Michigan State Univ., East Lansing, MI

**Abstract:** Metabolic processes are altered in cancer cells, and these changes are manifested in the volatile organic compound (VOC) composition of exhaled breath. Several studies using gas chromatography - mass spectrometry (GC-MS) and other engineered gas-sensing platforms indicate that individual VOCs can be up- or down-regulated due to cancer. However, due to the component-wise identification of VOCs used by GC-MS, it struggles to classify the entire complex mixture of thousands of low concentration VOCs present in human breath (parts-per-billion to parts-per-trillion range). Biological VOC sensing systems (olfactory sensory systems) are extremely sensitive, able to detect multiple volatile chemicals at low concentrations, and have evolved to classify complex mixtures found in natural environments. Here, we used an intact insect (honeybee) brain to harness the odor-evoked spiking responses of an olfactory neural circuit (antennal lobe) as a VOC sensor for lung cancer detection. The insect antennae,

analogous to vertebrate noses, contain sensory neurons that interact with VOCs. Signals from these sensory neurons travel to the antennal lobe in the insect brain, within which a biological spatiotemporal coding scheme is used to detect upwards of trillions of odor mixtures. To achieve our goals, we combined *in vivo* extracellular recordings from the antennal lobe with an electrophysiology platform and employed biological neural computation schemes of antennal lobe circuitry for data analysis. We analyzed electrophysiology recordings using both semi-automated spike sorting and fully automated root mean squared (RMS) filtering methodologies. Our results demonstrate that honeybees can reliably detect and distinguish nine different putative lung cancer biomarkers and can classify mixtures of these biomarkers that mimic exhaled breath samples of lung cancer patients and healthy subjects. To perform the classification analysis, responses from individual recording sites are combined to produce odor-evoked population neural response vectors that capture the spatiotemporal information encoded within the brain. A simple linear classifier using Euclidian distance and winner-take-all scheme achieved more than 85% accurate classification of cancer biomarkers. We also achieved 100% classification success of synthetic breath mixtures of lung cancer patients vs. healthy subjects, demonstrating that honeybee olfactory neuron response-based classification is sensitive and reliable. This study, along with our previous work using locusts to detect human oral cancer cell lines, provides a framework for the use of insect olfactory systems for cancer detection.

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**Poster**

**PSTR023. Olfaction: Central Mechanisms and Behavior I**

**Location:** WCC Halls A-C

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**Topic:** D.04. The Chemical Senses

**Support:** NSF Graduate Research Fellowship
NSF CAREER
MSU Startup Grant
NIH Grant HD099090

**Title:** Employing the locust olfactory system for the noninvasive detection of endometriosis

**Authors: *S. SANCHEZ**[1], M. PARNAS[1], E. VEGTER[2], Y. SONG[2], A. FAZLEABAS[2], D. SAHA[1];
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**Abstract:** Endometriosis is a gynecological disease characterized by the presence of endometrial tissue outside the uterus. It affects approximately 15% of reproductive age women and is associated with various non-specific symptoms. Definitive diagnosis is delayed an average of 7-

10 years after the onset of symptoms due to heterogeneity of symptoms and absence of specific biomarkers. Currently, laparoscopic surgery is the only acceptable method for the diagnosis of endometriosis and efforts to find non-invasive biomarkers have proved unsuccessful. The application of gas sensing technologies for the detection of endometriosis is rare, but has been used to noninvasively detect other metabolically linked diseases through the analysis of volatile organic compounds (VOCs). Several studies have utilized gas chromatography-mass spectrometry for the analysis of VOCs however this method uses a component-wise identification approach that is suitable for the identification of specific biomarkers. Since specific biomarkers have not been identified in the diagnosis of endometriosis, we carried out a non-specific approach to analyze VOC gas mixtures which may serve as an indicator of a diseased state within the body. Biological olfactory systems have evolved to detect minute differences in complex VOC mixtures in natural environments. Here, we address the challenge of detecting endometriosis noninvasively through a novel olfactory neuron-based sensor where we leverage the capacity of the entire biological olfactory sensory system of an insect brain (locust) and analyze neural responses to discriminate gas mixtures emitted from endometriotic vs. non-endometriotic cell lines. Our results demonstrate that this novel biosensing technology can discriminate between multiple types of endometriotic and non-endometriotic cell lines. For this study, VOC mixtures emitted from the cell cultures were delivered to the biological chemosensory array (antennae) and the neuronal responses (extracellular neuronal voltage signals) were obtained from the locust antennal lobe. Our analyses of cell culture headspace-evoked neural responses show that individual neurons can distinguish each cell line by its ‘smell’ (emitted VOC mixture). By combining the neural responses across experiments, we obtained high-dimensional population neural response templates that were used to classify unknown gas mixtures to achieve high classification accuracy. This innovative approach harnesses the full power of a biological olfactory system for the detection of endometriosis via VOC gas mixture analysis and lays the foundation for a novel detection tool to aid in the diagnosis of this disease.

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**Poster**

**PSTR023. Olfaction: Central Mechanisms and Behavior I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR023.14/W16

**Topic:** D.04. The Chemical Senses

**Support:** Israel Academy of Sciences and Humanities

**Title:** Learning-induced bidirectional enhancement of inhibitory synaptic metaplasticity

**Authors: *S. KUNDU**[1], B. PAUL[2], I. REUVENI[1], R. LAMPRECHT[1], E. BARKAI[1]; [1]Sagol Dept. of Neurobio., Univ. of Haifa, Haifa, Israel; [2]Dept. of Neurosci., Univ. of Texas, Dallas, TX

**Abstract: LEARNING-INDUCED BIDIRECTIONAL ENHANCEMENT OF INHIBITORY SYNAPTIC METAPLASTICITY**

Sankhanava Kundu, Blesson Paul, Iris Reuevni, Raphael Lamprecht and Edi BarkaiSagol
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Training rodents in a particularly difficult olfactory-discrimination (OD) task, results in acquisition to perform the task superbly, termed as 'rule learning'. Following learning, in addition to enhanced intrinsic cellular excitability and synaptic excitation in piriform cortex pyramidal neurons, rule learning results with increased synaptic inhibition too at whole circuity level to the point where it precisely maintains the balance between inhibition and excitation in the cortical network. The mechanism underlying such precise inhibitory enhancement is yet to be explored. Here we use brain slices from transgenic mice (VGAT-ChR2-EYFP), enabling optogenetic stimulation of single GABAergic neurons and recordings of unitary synaptic events in pyramidal neurons. Minimal stimulus experiments revealed that the calculated quantal size of the evoked inhibitory events in trainedanimal's neurons [12.2±4.1 pA, n=10] was significantly higher [$F_{2,26}$= 3.62, p=0.041] than controlanimal's neurons [naïve (8.9±2.1 pA, n=8), pseudotrained (8.7±2.8 pA, n=10)]. Next, we examined the plasticity of synaptic inhibition-induced longlasting intrinsically evoked spike firing in postsynaptic neuron. Repetitive depolarizing current pulses from resting (-70mV) or hyperpolarized (-90mV) membrane potentials induced long-term depression (LTD) and long-term potentiation (LTP) of synaptic inhibition, respectively. We found a profound bidirectional increase in the ability to induce both LTD (evoked responses were reduced by [-40.4% ±19.6, n=20] from trained gr. compared to naïve [-17.5% ±16.5, n=14] and pseudotrained [-19.1% ±16.5, n=13]), mediated by L-type $Ca^{+2}$ calcium channels and LTP (evoked responses were elevated by [28.0% ±32.5 (n=19)] for trained gr. compared to naïve [6.6% ±21.9, n=14] and pseudotrained [3.9% ±21.2, n=13]), mediated by R-type $Ca^{+2}$ channels. Blocking $GABA_B$-receptor reversed the effect of intrinsic stimulation at -90mV from LTP to LTD. In conclusion, we infer that intrinsic cellular adjustment for inhibitory inputs is bi-directionally strengthened following learning. Such cellular alteration allows fine tuning of inhibition on each principal neuron, thereby stabilizing the network to maintain the memory of rule learning.

**Disclosures: S. Kundu:** None. **B. Paul:** None. **I. Reuveni:** None. **R. Lamprecht:** None. **E. Barkai:** None.

**Poster**

**PSTR023. Olfaction: Central Mechanisms and Behavior I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR023.15/W17

**Topic:** D.04. The Chemical Senses

**Support:** ETRI/23YB1200
KBRI/22-BR-0502

**Title:** Investigating Mice's Behavioral Response to Predator Odors and Neural Correlations: A Wireless Monitoring Approach

**Authors: *H. LEE**[1], D. LEE[2], D. KIM[1], Y. LEE[2], K. KIM[2], S. LEE[1];
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**Abstract:** The olfactory sensory system, governed by the olfactory nerve (I) among the 12 pairs of cranial nerves emerging directly from the brain, is responsible for the sense of smell. This nerve facilitates the transmission of olfactory information from the nose to the brain, where it undergoes processing and interpretation. The sense of smell plays pivotal roles in taste, memory, and emotion, while also ensuring survival by aiding animals in detecting natural predators and potential threats. Many animals possess heightened olfactory senses, enabling them to detect predator scents and avoid danger. Smell also helps identify toxic substances or harmful elements like spoiled food or poisonous plants, enhancing animals' chances of survival. This research aims to examine mice's behavioral response to predator odors and correlate it with neural signals. We selected 2,4,5-trimethylthiazole (TMT), a compound derived from fox scent, as the olfactory stimulus. To facilitate unconstrained brain activity data collection and real-time brain activity analysis during unrestricted movement, we developed a customized wireless neural signal gathering system. This system, powered by a battery, incorporates an ARM Cortex-M4 microprocessor unit (MPU), an INTAN amplifier chip, and a Bluetooth module. We focused on monitoring the amygdala regions of the brain for neural signals. Understanding resting and seizure behaviors of mice in response to predator odors holds significant importance. In a 36 L volume box equipped with a video recording instrument, we placed 5 uL of TMT, alpha-pinene (ALP), and saline separately and introduced the mice. Their behaviors were analyzed using a Python-based movement tracking algorithm. Results showed a 35% higher occurrence of resting or seizure-like movements with TMT exposure compared to saline. However, exposure to 5 uL of ALP yielded similar resting or seizure-like movements as TMT exposure. Differentiating responses to TMT, representing predator odor, and ALP, disliked by mice, solely through behavioral analysis is challenging. Thus, we employed a wireless device to monitor and analyze the amygdala's local field potential, known for its involvement in fear perception as well as behavioral analysis such as occupancy and seizure-like movement together showing increased gamma oscillation during TMT exposure compared to ALP exposure. Our study is significant because it presents research methodologies for both individual responses to particular odors as well as various situation of social interaction behavior of multiple individuals to various odors.

**Disclosures: H. Lee:** None. **D. Lee:** None. **D. Kim:** None. **Y. Lee:** None. **K. Kim:** None. **S. Lee:** None.

**Poster**

**PSTR024. Taste**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR024.01/W18

**Topic:** D.04. The Chemical Senses

**Support:** R01 DC013770
UF1 NS115779

**Title:** Gastrin Releasing Peptide Receptors Modulate Gustatory Cortex Circuits Excitability and Function

**Authors: *M. ISAAC**[1], C. FONTANINI[2], A. MAFFEI[2];
[1]Stony Brook Univ., Port Jefferson Station, NY; [2]Neurobio. and Behavior, Stony Brook Univ., Stony Brook, NY

**Abstract: Gastrin Releasing Peptide Receptors Modulate Gustatory Cortex Circuits Excitability and Function***Maria Isaac[1,2], Carlo T. Fontanini[1] and Arianna Maffei[1,2]*1-*Department of Neurobiology and Behavior; 2- Graduate Program in Neuroscience, Stony Brook University, Stony Brook, NY*
Eating is a dynamic process driven by internal states, sensory and visceral information, and experience-based associations formed with food. The study of appetite regulation primarily focuses on hypothalamic circuits, although recent evidence points to the gustatory insular cortex (GC) as a fundamental component of feeding behavior. Gastrin releasing peptide (GRP), a neuropeptide that is highly expressed in the gustatory cortex (GC), induces meal termination in human and animal studies, when injected systemically. GRP signals through gastrin releasing peptide receptors (GRPRs), but the neurons expressing GRPRs in the gustatory system have not been identified. Furthermore, the role of GRP in modulating the native circuit within the GC remains unexplored. Here we used a transgenic mouse line labeling GRPR-expressing cells and report that they are enriched in GC. GRPR-GC cells comprise a histologically heterogenous population of neuronal cells. This heterogeneity was further verified by in situ hybridization and analysis of membrane properties using patch clamp recordings in acute slice preparations. Comparison of the prevalence of GRPR cells between male and female mice revealed a larger prevalence of GRPR expressing cells in males, unveiling possible sex differences in GRP signaling. Electrophysiological recordings showed that bath application of GRP substantially increases inhibitory drive onto GRPR expressing cells. Additionally, GRP application decreases excitatory drive onto GRPR expressing cells, while increasing it in GRPR- neurons. These results show that satiety signals like GRP exert a powerful influence on GC by engaging diverse populations of cells largely by increasing inhibition on GRPR positive cells.

**Disclosures: M. Isaac:** None. **C. Fontanini:** None. **A. Maffei:** None.

**Poster**

**PSTR024. Taste**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR024.02/W19

**Topic:** D.04. The Chemical Senses

**Support:** NIH Grant DC019518

**Title:** Extrasynaptic $GABA_A$receptors in the gustatory cortex and taste-dependent behavior

**Authors: *P. YEVOO**, A. FONTANINI, A. MAFFEI;
Stony Brook Univ., Stony Brook, NY

**Abstract:** The gustatory cortex (GC) - a portion of the insular cortex - processes taste, reward expectation, and decisions about food intake in adults, making it a relevant model for studying cortical mechanisms underlying feeding behaviors. Structural and chemical anomalies in the insular cortex have been associated with dysfunctional eating. The Gabaergic system regulates food intake, but the substrates for this modulation are unknown. Here we test the hypothesis that altered tonic, neurosteroid-modulated, GABAergic inhibition levels in GC contribute to taste-dependent impulsive choices, using the neurosteroid allopregnanolone and analyzing consummatory behavior and GC circuit excitability. We assessed the effect of local neurosteroid infusion in GC on sucrose preference and showed an increase in sucrose preference. This increase was associated with a neurosteroid-induced alteration of the animals' approach to food in a Go/No-Go task. To determine the neural mechanisms underlying the effects of allopregnanolone, we examined the patterns of expression of δ-$GABA_A$Rs, the primary target of this neurosteroid, and report that these receptors are localized in different proportions on the somata of both inhibitory and excitatory neurons in GC. To explore the receptor's functionality, we employed patch-clamp recordings from neurons in acute slices to test the magnitude of tonic inhibitory currents. Our data show an increase in tonic currents following allopregnanolone application. Our findings reveal that increased sucrose preference is associated with changes in motivation to consume. This data supports the hypothesis that GC plays a central role in controlling ingestive behaviors and that tonic inhibition is a likely mechanism for controlling food-seeking behavior. Understanding the mechanisms underlying inhibitory control deficits will provide novel biomarkers for diagnosing, treating, and preventing neuropsychiatric disorders characterized by impaired motivational states and inhibitory control.

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**Poster**

**PSTR024. Taste**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR024.03/W20

**Topic:** D.04. The Chemical Senses

**Support:** R01DC018227
R21DC017681

**Title:** Taste processing in a mouse model of Frontotemporal Dementia

**Authors: *Y. ZHENG**[1,2,3], J. BLACKWELL[1], A. FONTANINI[1];
[1]Stony Brook University, Neurobio. & Behavior, Stony Brook, NY; [2]Stony Brook University,

Program in Neurosci., Stony Brook, NY; [3]Stony Brook University, Med. Scientist Training Program, Stony Brook, NY

**Abstract:** Frontotemporal dementia (FTD) is the second most prevalent form of presenile dementia. Patients with FTD show a pathological sweet tooth and decreased ability to identify flavors. Taste perception depends on neural processing in chemosensory regions such as the insular cortex - a brain region that also contains the primary taste cortex, gustatory cortex (GC). The chemosensory deficits in FTD may be related to GC damage as insular cortex is one of the primary targets in FTD disease progression. Little is known on how circuitry changes related to FTD lead to abnormal activation of GC and to deficits in taste processing in FTD. The goal of this project is to test the hypothesis that the chemosensory deficits in a mouse model of FTD are related to abnormal patterns of neural activity in GC. TDP-43 inclusions are a significant pathological feature in 50% of FTD cases, thus we use a transgenic mouse model overexpressing human transactivating response region (TAR) DNA binding protein (TDP-43) with a Q331K mutation (Q331K mutants) To assess chemosensory deficits, we relied on a taste-based two alternative forced choice (2AFC) task probing the ability to discriminate sucrose/NaCl mixtures. Q331K mutants make more mistakes and show significant deficits in the mixture discrimination 2AFC task. To monitor neural activity, we relied on electrophysiological recordings using chronically implanted tetrodes in alert Q331K mutants and control mice. Activity in GC was probed as mice licked multiple gustatory stimuli (sucrose 200mM, sodium chloride 50mM, quinine 0.5mM, citric acid 10mM). Classification analysis shows that taste decoding decays faster in Q331K mutant mice relative to control mice. Principal component analysis confirms that population activity dynamics evoked by the different gustatory stimuli are more similar in Q331K mutants than in control mice. Overall, these results demonstrate taste deficits in a mouse model of FTD and provide evidence for altered taste processing in GC of Q331K mutants compared to control mice.

**Disclosures: Y. Zheng:** None. **J. Blackwell:** None. **A. Fontanini:** None.

**Poster**

**PSTR024. Taste**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR024.04/W21

**Topic:** D.04. The Chemical Senses

**Support:** F32-DC018485
R01-DC015234

**Title:** Postnatal development of gustatory cortical circuits

**Authors: *H. C. SCHIFF**[1], A. MAFFEI[2];
[1]Neurobio. & Behavior, SUNY - Stony Brook, Stony Brook, NY; [2]Neurobio. and Behavior, SUNY Stony Brook, Stony Brook, NY

**Abstract:** Cortical circuits for sensory systems undergo protracted maturation during the postnatal period. This circuit refinement is sensitive to experience and ultimately supports complex functions like perception and cognition. The gustatory insular cortex (GC), the primary sensory region for taste, regulates taste-based behaviors including taste preference, decision making and memory formation. At weaning, animals transition from relying on their mother's milk to foraging for food, experiencing an abundance of novel tastes. This early taste experience influences the development of taste preferences. However, there is very little information regarding the time course of circuit maturation in GC. Here we used whole-cell patch-clamp electrophysiology, immunohistochemistry, and neuronal reconstructions to track postnatal changes in GC of male and female mice. In GC pyramidal neurons, we found an increase in spontaneous inhibitory postsynaptic currents (IPSCs) and no relative change in spontaneous excitatory postsynaptic currents (EPSCs) from pre-weaning to early adult ages, suggesting developmental regulation of the excitatory-to-inhibitory ratio. The changes in synaptic inhibition were accompanied by increases in parvalbumin (PV) fluorescence intensity in PV-expressing interneurons ($PV^+$ INs) and accumulation of perineuronal nets on $PV^+$ INs. We also observed morphological changes in pyramidal neurons, and a temporary decrease in excitability. These results suggest that maturation of GC circuits are largely associated with maturation of $PV^+$ INs, and that these developmental processes may be sensitive to taste experience. We are currently mapping the local connectivity of inhibitory synapses onto pyramidal neurons and assessing how connectivity patterns and dynamics of these synapses change across postnatal development.

**Disclosures: H.C. Schiff:** None. **A. Maffei:** None.

**Poster**

**PSTR024. Taste**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

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**Topic:** D.04. The Chemical Senses

**Support:** NIH F30DC019523
NIH R01DC018227
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NIH R01DC013770

**Title:** Discrimination learning leads to enhanced representation of taste-guided decisions in the mouse gustatory insular cortex

**Authors: *J. KOGAN**, A. FONTANINI;
Neurobio. and Behavior, Stony Brook Univ., Stony Brook, NY

**Abstract:** The ability to discriminate between overlapping sensory stimuli is essential for survival. This phenomenon, known as discrimination learning, has been extensively studied in the visual, auditory, somatosensory, and olfactory systems, using operant tasks paired with

neural recordings in behaving animals. Discrimination learning is especially important in the case of taste, where it could mean the difference between ingesting a nutritive meal and a poison. Despite this, few studies have addressed the mechanisms of taste discrimination learning. Based on work in other sensory systems, two general mechanisms have been proposed; i) sharpening of sensory representations or ii) enhanced ability of "higher-order" decision-making circuits to interpret sensory evidence. Importantly, these mechanisms are not mutually exclusive. The gustatory insular cortex (GC) plays an important role in mediating ingestive choices by encoding both sensory and decision-related information in time-varying patterns of neural activity, but its role in taste mixture discrimination remains unclear. To study the role of GC in discrimination learning, six head-fixed mice were trained to perform a taste mixture discrimination two alternative choice (2-AC) task. Two photon calcium imaging was used to record neural activity as mice learned to discriminate between increasingly similar pairs of taste mixtures. The task includes a delay epoch to separate sensation from action, allowing for examination of the evolution of neural responses across task trials. Single neuron and population decoding analysis demonstrate early sensory responses emerging directly after stimulus presentation, with binary responses to the upcoming choice emerging later in the delay. Further, after extensive training on the mixture discrimination task, a selective enhancement of decision-related responses in the delay was observed. These results demonstrate that while both sensory and decision-related information is encoded in GC ensembles in the context of a taste-mixture discrimination task, learning and improved performance is associated with a specific enhancement of decision-related responses.

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**Poster**

**PSTR024. Taste**

**Location:** WCC Halls A-C

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**Topic:** D.04. The Chemical Senses

**Support:** SSTF-BA2002-14
2019M3E5D2A01058329
2020R1A5A1018081

**Title:** Glia-like taste cells mediate a paracrine mode of peripheral sweet adaptation

**Authors: *G. PARK**[1,2], G. LEE[1,2], J. HAN[3], P. CHOI[3], M. KIM[1,2], C. PARK[1,2], Z. WU[4], Y. LI[4], M. CHOI[1,2];
[1]Seoul Natl. Univ., Seoul, Korea, Republic of; [2]The Inst. of Mol. Biol. and Genet., Seoul, Korea, Republic of; [3]Korea Brain Res. Inst. (KBRI), Daegu, Korea, Republic of; [4]Peking Univ., Beijing, China

**Abstract:** As present in diverse levels of sensory information processing, perceived sweetness to prolonged exposure of sweet compounds declines over time. This so-called sweet adaptation has long been known to be mediated by the internalization of sweet receptors at the apical tip of taste buds. Here, we report that there is an alternative mode of sweet adaptation occurring within the taste bud, possibly mediated by intercellular interaction between glia-like type I and sweet-sensing type II cells. First, exploiting volumetric microscopy on fungiform taste buds in vivo, we revealed that the downstream afferent nerve terminals exhibit a higher degree of sweet adaptation compared to the upstream type II cells. Next, we identified that purinergic crosstalk from type II to type I cells is mediated by a specific subtype of P2Y receptor. Pharmacological activation of type I cells resulted in significant attenuation of taste-evoked ATP release from type II cells and neural calcium activity in the afferent nerves, indicating that type I cells provide inhibitory modulation to the peripheral transduction of sweet information. Taken together, our results substantiate that peripheral sweet adaptation is not only mediated by receptor internalization, but also by intercellular crosstalk between type II and type I cells.

**Disclosures:** **G. Park:** None. **G. Lee:** None. **J. Han:** None. **P. Choi:** None. **M. Kim:** None. **C. Park:** None. **Z. Wu:** None. **Y. Li:** None. **M. Choi:** None.

**Poster**

**PSTR024. Taste**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR024.07/W24

**Topic:** D.04. The Chemical Senses

**Support:** SSTF-BA2002-14
2019M3E5D2A01058329
2019M3A9E2061789
RGY0068/2020

**Title:** Binary taste interaction in mouse geniculate ganglion

**Authors: *C. PARK**[1,2], J. YOON[1], M. CHOI[1,2];
[1]Sch. of Biol. Sci., Seoul Natl. Univ., Seoul, Korea, Republic of; [2]Sch. of Biol. Sci., The Inst. of Mol. Biol. and Genet., Seoul, Korea, Republic of

**Abstract:** Geniculate ganglion houses cell bodies of pseudounipolar neurons that relay taste information from the tongue to the brain. As a relay station, geniculate neurons are known to respond on time to orally delivered taste stimuli to transfer taste identity to the brain in a timely manner. To reliably record neuronal responses to taste stimuli, we surgically secured optical access to the geniculate ganglion in an anesthetized mouse and performed widefield calcium imaging on it while controllably delivering taste substances on the anterior tongue. We used six single taste substances (sweet, bitter, sour, umami, low salt, high salt) and all possible binary combinations of six single tastes to see whether interaction between tastes affects the neurons in

a geniculate ganglion. Intriguingly, we observed that simply averaging calcium responses responding to each single taste wasn't fully fit with calcium responses responding to binary taste mixtures, implying synergistic/antagonistic interaction between specific tastes initiates from peripheral nervous systems. As we consume tastes in a form of mixture of various tastes rather than a form of single taste substances in our daily life, robust in vivo imaging of geniculate ganglion enables us to infer the expected sensation of a specific combination of tastes without direct foretaste.

**Disclosures: C. Park:** None. **J. Yoon:** None. **M. Choi:** None.

**Poster**

**PSTR024. Taste**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR024.08/W25

**Topic:** D.04. The Chemical Senses

**Support:** R01 DC18733 (SDR and NC)
R01 DC006308 (NC)

**Title:** Plcb2 independent detection of glucose in gustatory afferent neurons

**Authors: *Y. A. RODRIGUEZ**[1], E. PEREIRA[1], G. DVORYANCHIKOV[1], G. E. HARDEN[1], S. D. ROPER[1,2], N. CHAUDHARI[1,2];
[1]Physiol. and Biophysic, Univ. of Miami, Miami, FL; [2]Otolaryngology, Univ. of Miami Miller Sch. of Med., Miami, FL

**Abstract:** Sweet, bitter and umami tastes are transduced via taste GPCRs and a signaling cascade that includes phospholipase Cβ2 (PLCβ2). In addition, glucose and certain sugars are believed to act on taste cells via transmembrane transporters, independent of GPCRs and PLCβ2, and stimulate cephalic phase insulin release (CPIR). We tested a panel of sugars and an artificial sweetener to determine if any might evoke PLCβ2-independent responses in gustatory neurons of the geniculate ganglion *in vivo*. We recorded taste-evoked $Ca^{2+}$ responses in geniculate ganglion neurons in male and female *Plcb2*$^{-/-}$ (ko) mice or heterozygous littermates in which GCaMP3 is expressed in sensory neurons. As expected, taste-evoked responses to brief exposure (5 sec) of NaCl (250 mM) or citric acid (10 mM) showed no significant difference between *Plcb2* ko and heterozygous mice (p=0.85 and 0.09, respectively; n=7 ko, 6 het; Mann-Whitney). By contrast and as expected, brief taste stimulation with 300mM sucrose or a bitter mixture (0.3 mM quinine, 1 μM cycloheximide) rarely elicited responses in *Plcb2* ko mice. Yet, to elicit CPIR, experimenters use long duration stimulation (≥ 30 sec) and high concentrations (up to 1M) of sugars. Thus, we applied 30 sec stimulation with 1M glucose, maltose, sucrose, or fructose, or 15 mM AceK. Under these conditions, responses to these sweeteners were now observed in *Plcb2* ko mice, albeit often not as large as those in het mice. Importantly, responses to 1M glucose were not significantly different between *Plcb2* ko and heterozygous mice (glucose p= 0.11; other

sweeteners p=0.01 to 0.02; Mann-Whitney
test). As a control, we recorded responses to brief (5 sec) application of high concentrations of sweeteners, presented for only 5 sec. We observed very few responses in *Plcb2* ko mice, a dramatic difference from heterozygous mice. In summary, responses in gustatory afferent neurons to extended stimulation with glucose, the primary trigger for CPIR, are similar between *Plcb2* ko and heterozygous mice, suggesting that glucose is detected via a non-GPCR/*Plcb2* transduction pathway. In contrast, the data are consistent with the other sweeteners we tested being detected through canonical GPCR/*Plcb2* transduction, as extensively documented.

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**Poster**

**PSTR024. Taste**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR024.09/W26

**Topic:** D.04. The Chemical Senses

**Support:** An intramural grant to MS

**Title:** Tastant-evoked oscillatory responses in the primary taste center of Manduca sexta

**Authors: *A. BORONAT-GARCÍA**[1], S. REITER[2], M. A. STOPFER[1];
[1]Section on Sensory Coding and Neural Ensembles, NICHD-NIH, Bethesda, MD; [2]Okinawa Inst. of Sci. and Technol. Grad. Univ., Okinawa, Japan

**Abstract:** Understanding how sensory systems drive behavior requires knowledge about the identity, connectivity, and response patterns of the population of neurons involved in detecting, transforming, and integrating sensory information. Gustation, despite its medical and physiological importance, is the least understood of the main sensory systems. The moth Manduca sexta is an excellent model for studies of gustation. It has a relatively simple nervous system yet exhibits complex gustatory behaviors, allows for electrophysiological recordings, and the analysis of multiple brain regions in awake animals while presenting real taste stimuli. Previous work showed that gustatory sensory neurons (GSNs) in the periphery and second order neurons (SONs) in the primary taste brain center, the sub-esophagus zone (SEZ), use a population code to represent individual taste chemicals rather than broad taste categories (Reiter et al, 2015). However, it is still unclear how taste information is transformed as it moves to other brain areas. To further understand this process, we combined anatomical and electrophysiological approaches. To assess the possibility that tastes elicited coordinated population activity, we recorded local field potentials (LFPs) from the SEZ while presenting pulses of tastants to the proboscis (Boronat et al, 2017). Taste pulses elicited strong, regular LFP oscillations of ~ 20-50 Hz, with a peak at ~40 Hz. Recordings with sharp intracellular electrodes made from SONs revealed taste-elicited oscillatory responses in the membrane potentials of

these neurons that correlated with those in simultaneously recorded LFPs. Further, taste-induced oscillations were reversibly and significatively reduced or abolished by injecting picrotoxin, a GABA antagonist, but not saline, into the SEZ, suggesting inhibitory neurons may participate in coordinating the oscillatory activity. These findings emphasize the complexity of the gustatory circuit. However, several important questions remain unanswered, such as the role, if any, played by this pattern of activity in processing gustatory information. Our studies will provide a more comprehensive understanding of the gustatory system.

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**Poster**

**PSTR024. Taste**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR024.10/W27

**Topic:** D.04. The Chemical Senses

**Title:** Gustatory processing within and beyond the suboesophageal zone in Drosophila

**Authors: *L. PAPPALARDO**[1,2], Y.-S. HUNG[1], M. STOPFER[1];
[1]Eunice Kennedy Shriver Natl. Inst. of Child Hlth. and Human Development, Section on Sensory Coding and Neural Ensembles, NIH, Bethesda, MD; [2]Cell, Molecular, Developmental Biology, and Biophysics, Johns Hopkins Univ., Baltimore, MD

**Abstract:** Gustation (the sense of taste) is essential for distinguishing nutritious foods from toxins and enhancing quality of life. Yet, the mechanisms underlying gustation are still debated. There are two main hypotheses about how gustatory signals are encoded: 1) labeled line, which posits that relatively few taste categories exist and are encoded by parallel, independent paths through the brain, and 2) combinatorial codes, which suggests that tastes, potentially of many kinds, are encoded by combinations of simultaneously active neurons that each respond to multiple tastes. Results obtained from the moth Manduca sexta indicate first and second-order gustatory neurons use a combinatorial coding mechanism. Here, we test these ideas in *Drosophila melanogaster* because it allows for comprehensive and reproducible experiments to address this controversy at the level of single, identifiable neurons. Because the labeled line idea specifies pathways for different tastes will not converge, we used anatomical and physiological approaches to test for the convergence of multiple types of first-order gustatory receptor neurons (GRNs). We focused on an identified second-order suboesophageal zone (SEZ) interneuron G2N-1 (Miyazaki et al, 2015). First, with GFP Reconstitution Across Synaptic Partners (GRASP), we found that G2N-1 receives direct input from GRNs expressing receptors PPK23 (responds to high concentrations of salt and bitter tastants), PPK28 (responds to water or low concentrations of salt) and GR64f (responds to sugars). Next, we stimulated neurons expressing GR64f or PPK28 optogenetically, and, using calcium imaging, found that G2N-1 responded. And finally, we showed that G2N-1 is activated when pulses of high concentration sucrose or high concentration NaCl are delivered to the fly's proboscis. To understand how responses of

second-order neurons are processed downstream we are seeking their follower neurons. Recent research points to several brain regions that could function as third order gustatory processing areas. We focused on the superior medial protocerebrum and superior lateral protocerebrum. We are exploring the connectivity to these two regions using TransTango. Together, these experiments will provide a more comprehensive view of how the gustatory system encodes taste.

**Disclosures: L. Pappalardo:** None. **Y. Hung:** None. **M. Stopfer:** None.

**Poster**

**PSTR024. Taste**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR024.11/W28

**Topic:** D.04. The Chemical Senses

**Support:** NIDCD grant RO1 DC006914

**Title:** Gustatory modulation of electrophysiological responses to food in the nucleus tractus solitarius of the awake, unrestrained rat

**Authors:** S. A. PILATO, F. P. O'CONNELL, ***P. M. DI LORENZO**;
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**Abstract:** Electrophysiological recordings in the gustatory portion of the nucleus tractus solitarius (NTS) have revealed that both taste-responsive and motor-related cells respond to exploration of solid food. Further, when a rat engages with food, the firing patterns of NTS cells align in a predictable way, suggesting an organizational shift. Moreover, many cells respond in anticipation of contact with food, prior to any contact. We hypothesized that this orderly alignment, as well as the anticipatory (potentially olfactory) activity, may be directed by cortical input. To test this hypothesis, we optogenetically silenced the projections of the gustatory cortex (GC) to the NTS just before the rat enters a “well” filled with solid food. Initially, an adeno-associated viral construct encoding halorhodopsin-EYFP (eNphR3.0) was infused unilaterally into the GC. Rats were later implanted with a drivable microelectrode bundle in the ipsilateral NTS and allowed to recover. An experimental chamber contained a variety of solid foods placed in the wells positioned at the corners. Custom software defined invisible “zones” surrounding two of the wells where a breach of the zone triggered a train of laser pulses that remained on until the rat’s head left the well. A 589 nm laser was used to inhibit GC terminals in the NTS. Following each trigger, a pulse train (15ms pulses, 25Hz, 8-10 Watts) was delivered through the tip of the fiberoptic. The remaining two wells were filled with matching foods but well entry did not trigger the laser. Foods were dark chocolate (90% cacao), milk chocolate chips (37% cacao), Granny Smith apples or salted peanuts. An infrared beam across the entrance to each well recorded well entry and exit. Food sessions were videotaped and scored offline for eating. Results from 12 NTS cells showed that silencing GC input to the NTS as the rat approached a food well had effects that varied across cells. These effects included: suppressing the number of

laser-associated well entries, enhancing or attenuating the response to well entry for some foods and/or shortening the anticipatory response to well entry. In addition, GC-NTS silencing modulated high frequency (60-100 Hz) activity associated with approach and entry of the head in the well. This result may reflect a disruption of upstream communication about food. Collectively, these data suggest that GC input to the NTS exerts a subtle but consequential organizational effect on the neural responses to appetitive and consummatory behavior. In addition, effects of GC-NTS silencing on NTS responses prior to well entry suggests that the GC may be delivering food-related olfactory input to the NTS to hone food acceptance or rejection.

**Disclosures: S.A. Pilato:** None. **F.P. O'Connell:** None. **P.M. Di Lorenzo:** None.

**Poster**

**PSTR024. Taste**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR024.12/X1

**Topic:** D.04. The Chemical Senses

**Support:** Samsung Science and Technology Foundation Grant SSTF-BA2002-14
NRF of Korea Grant 2020R1A5A1018081

**Title:** Sweet off-response in type III taste cells

**Authors: *G. LEE**[1,2], M. CHOI[1,2];
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**Abstract:** Type III cells in the taste buds are known for encoding sour taste, as well as sensing of water taste. Here we report a novel functional role of type III cells in encoding of sweet off-response. Using in vivo functional imaging of genetically-targeted type III cells in fungiform taste buds, we observed that a subpopulation of sour-sensing type III cells exhibits calcium activity in response to sweet offset, but not the onset, amidst the termination of prolonged sweet stimuli. The longer duration of sweet stimuli was more effective in evoking the sweet off-response, implying the existence of an underlying cumulative phenomena. Pharmacological inhibition experiments suggested that hyperpolarization of type III cells, which is analogous to the mechanism of off-response auditory neurons, underlies the sweet off-response. Taken together, these results may indicate that taste buds are capable of generating secondary signals through cellular interaction.

**Disclosures: G. Lee:** None. **M. Choi:** None.

**Poster**

**PSTR024. Taste**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

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**Topic:** D.04. The Chemical Senses

**Support:** Lauria STEM Research Scholarship (CMM & MJW)
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**Title:** Early-life ingestion of non-nutritive sweetener associated with lowered expression of sweet taste cell markers in the circumvallate lingual epithelium and smaller circumvallate taste bud field size in adult rats.

**Authors: M. J. WITT**[1], S. CHOMETTON[2], S. J. TERRILL[3], L. A. SCHIER[2], *C. M. MATHES[1];
[1]Neurosci., Baldwin Wallace Univ., Berea, OH; [2]Biol. Sci., USC, Los Angeles, CA; [3]Neurosci., Carthage Col., Kenosha, WI

**Abstract:** Non-nutritive sweeteners (NNS) are promoted as healthier choices than sugar, but they may have negative long-term health impacts, especially when consumed during critical developmental periods. We previously found that food-restricted rats exposed early in life to NNS lick fructose more avidly than unexposed rats and have lower expression of one of the sweet taste receptor genes, *Tas1r3*, in the lingual epithelium of their tongue that contains the circumvallate (CV) papillae. This could be accompanied by other expression and/or structural differences in the CV taste field. Thus, here we assessed differences between rats exposed early in life to NNS and unexposed control rats in terms of 1) expression of SGLT1 (a glucose transporter), GLUT5 (a fructose transporter), PLCβ2 (a marker of Type-II taste cells), and SHH (indicative of taste cell maintenance) in the previously analyzed tissue, and 2) span and taste bud density of the CV in three phases of other rats. Male and female rats were from postnatal day (PND) 26-76 given daily access to the NNS acesulfame potassium (AceK; 0.1% at 15 ml/kg); another group of rats received no AceK and served as the control group (CNTL). After PND 76, rats were allowed to age until ~PND 220. Some rats were euthanized at ~PND220 and others were euthanized after behavioral taste-testing protocols at ~PND300. The lingual epithelium containing the CV was extracted from some rats, and other rats were transcardially perfused, after which their CV was sliced coronally on a cryostat (20 µm). The lingual epithelium was run through qPCR, and the sliced tissue was mounted on slides, Nissl stained, and the number of slices of CV that contained taste buds and the number of buds in two slices halfway rostral and caudal to the midpoint of the CV were quantified (viewed at 10x by an experimenter blind to group). GLUT5, PLCβ2, and SHH mRNA expressions were significantly lower in food-restricted NNS rats (n=5), compared to CNTL rats (n=6). NNS rats (n=8) also had fewer slices across the CV field than did CNTL rats (n=5), although this was only analyzable in male rats, which is pertinent because female CNTL rats (n=5) also had smaller CV fields than did male CNTL rats (n=5). No differences due to early-life NNS exposure was seen in terms of the number of taste buds in the slices analyzed or in SGLT1 expression. This suggests that early-life NNS ingestion lowers mRNA expression of multiple aspects of taste machinery and, at least in males, decreases CV field size. Overall, these data align with our previous data and further

suggest that early-life exposure to NNS has long lasting impacts on taste-based behavior and physiology.

**Disclosures:** **M.J. Witt:** None. **S. Chometton:** None. **S.J. Terrill:** None. **L.A. Schier:** None. **C.M. Mathes:** None.

**Poster**

**PSTR024. Taste**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR024.14/X3

**Topic:** D.04. The Chemical Senses

**Support:** R01 DC20212

**Title:** Taste responses in the gustatory cortex of freely moving neonatal rats

**Authors: *T. V. DONG**, J. X. MAIER;
Neurobio. and Anat., Wake Forest Univ. Sch. of Med., Winston-Salem, NC

**Abstract:** How animals use sensory information changes throughout development. This is especially clear during the first few weeks of life as new behaviors arise. These behavioral changes often occur as discrete shifts. Work in other sensory areas suggests that the rapid onset of new behaviors is preceded by changes in neural circuits. To determine if this principle can be applied to the taste system, we examined taste responses in the rat gustatory cortex around weaning age. Weaning is an essential developmental timepoint for many animals because it requires a dramatic shift from full dependence on the dam to active food exploration. This behavior requires a functional taste sense, but it has not been determined whether the development of gustatory processing precedes weaning or how neonatal taste responses compare to mature processing. To examine how changes in cortical taste processing relate to this behavioral transition, we recorded responses to passively presented taste stimuli from the gustatory cortex of awake, freely moving, neonatal rats between P13 and P19. Multielectrode arrays and intraoral cannulas (IOCs) were chronically implanted at ages ranging from P12 to P17 with daily recordings starting the day after surgery. Both local field potentials and single unit taste responses were obtained and analyzed. We found circuit-level activity patterns with several mature features, including taste-evoked event related potentials and 20-40 Hz induced oscillations, as well as a nonspecific increase in power at frequencies above 60 Hz with respect to baseline. Response patterns were taste-specific, and observed in animals as young as P13, well before the onset of foraging. This suggests that the gustatory cortex acquires mature features at a relatively early age with respect to the behavioral transition from suckling to active food exploration around P18.

**Disclosures:** **T.V. Dong:** None. **J.X. Maier:** None.

**Poster**

**PSTR024. Taste**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR024.15/X4

**Topic:** D.04. The Chemical Senses

**Support:** NIDDK Grant 3R01DK125081

**Title:** Neuropeptide Y Family Peptides Differentially Modulate the Functional Responses of Human Taste Bud Cells

**Authors: *S. IYER**, J.-P. R. MONTMAYEUR, C. S. DOTSON;
Georgia State Univ. Neurosci. Inst., Atlanta, GA

**Abstract:** Obesity and related metabolic disorders have been linked to the dysregulation of food intake. Several gut peptides have been implicated in the mediation of feeding behaviors and the accumulation of body mass. These circulating peptides influence appetite through their actions on the hypothalamus, the brain stem, and the autonomic nervous system. The powerful influence of these peptides on food intake and the accumulation of body mass underscores their potential value as treatments for obesity and related metabolic disorders. In previous reports, we have shown that the hormone peptide YY (PYY), a member of the Neuropeptide Y family of peptides, is present in the saliva of both humans and mice and that the augmentation of salivary $PYY_{(3-36)}$, using either genetic or pharmacological approaches, affects taste responsiveness, as well as food intake and body weight in diet-induced obese mice. However, it is unknown exactly how these peptides, when present in saliva, impact upon this responsiveness. Indeed, a significant number of metabolic polypeptides, including those of the Neuropeptide Y family, have been shown to be present in saliva or expressed in taste bud cells (TBCs). The presence of these peptide signaling systems either in or near to tissues of the peripheral gustatory system suggests that these compounds may play a role in modulating TBC function and potentially, the propagation of taste information to the CNS. As such, we assessed whether specific metabolic peptides could directly impact upon the functioning of TBCs by measuring the response properties (via calcium imaging and adenosine triphosphate release measurements) of human fungiform TBCs in culture, stimulated with prototypical taste stimuli, in the presence or absence of these peptides. Data from these experiments suggest that the responses of human TBCs themselves are differentially modulated by Neuropeptide Y family peptides; for example, bitter-evoked ATP release was significantly augmented by NPY exposure but significantly suppressed by $PYY_{(3-36)}$ exposure ($p < 0.05$, ANOVA). This work provides compelling new evidence supporting the hypothesis that the gustatory periphery can be dynamically modulated in the context of an animal's metabolic state and/or environmental circumstance.

**Disclosures: S. Iyer:** None. **J.R. Montmayeur:** None. **C.S. Dotson:** None.

**Poster**

**PSTR024. Taste**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR024.16/X5

**Topic:** D.04. The Chemical Senses

**Support:** Productos Medix 3247
CONACyT Grants Fronteras de la Ciencia CF-2023-G-518

**Title:** Obesity alters GABAergic neuron activity in the lateral hypothalamus

**Authors: *M. LUNA**, A. COSS, O. X. GUERRERO-GUTIERREZ, R. GUTIERREZ;
Pharmacol., CINVESTAV, Gustavo A. Madero, Mexico

**Abstract:** Obesity is a global health issue that has been linked to several factors, including overconsumption beyond homeostatic needs promoted by the taste and high palatability of added sugars. The Lateral Hypothalamic Area (LHA) is a brain region that has been implicated in the regulation of feeding behavior. Studies have shown that obesity can affect the transcriptional profile of LHA glutamatergic neurons, weakening their activity and leading to overeating and obesity. However, it is not yet clear how diet-induced obesity alters the activity of GABAergic LHA neurons in response to the palatability of sucrose. To address this question, we used a Vgat-IRES-Cre mouse model to express the calcium indicator GCaMP6m in GABAergic neurons in the LHA. We divided the mice into a diet-induced obesity group (HDF: fed with High-Fat Diet) and a reference group (CHOW: fed with a normal chow diet). We then used in vivo microendoscopic recordings to measure $Ca^{2+}$ activity from individual GABAergic neurons in response to a brief access taste test (BATT). The BATT comprised a 4-second reward period during which mice could lick a sipper to receive an empty sipper, water, 3%, or 18% sucrose. The average number of licks per second (lick rate) and the size of the bouts (bursts of rhythmic licks separated by a pause of at least 0.5 s) were used as direct measures of oromotor palatability responses. We found that $LHA^{Vgat}$ neurons from HFD mice became progressively more responsive to the most palatable option (18% sucrose) over the 12-week study period. This suggests that diet-induced obesity can lead to increased sensitivity of GABAergic LHA neurons to the palatability of sucrose, which may contribute to the development of obesity. Our findings provide new insights into the neural mechanisms underlying the development of obesity. Further research is needed to determine whether targeting GABAergic LHA neurons could be a potential therapeutic strategy for the treatment of obesity.

**Disclosures: M. Luna:** None. **A. Coss:** None. **O.X. Guerrero-Gutierrez:** None. **R. Gutierrez:** None.

**Poster**

**PSTR024. Taste**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR024.17/X6

**Topic:** D.04. The Chemical Senses

**Support:** R01DC000407

**Title:** Injury-induced plasticity of taste nerve terminal fields in the mouse NST produced by a sensitizing chorda tympani nerve cut at adulthood

**Authors: *C. SUN**, D. L. HILL, A. ERISIR;
Psychology, Univ. Virginia, Charlottesvle, VA

**Abstract:** Injury-induced plasticity of central terminal fields occurs in multiple sensory systems when peripheral nerves are cut or damaged at adulthood. However, this plasticity induced at adulthood is not universal. Indeed, the occurrence of the effects appears to relate to the inherent plasticity of the specific sensory system. Moreover, an initial injury to a peripheral nerve may cause a supersensitive response when the nerve is injured later. We show here that a similar phenomenon occurs for the central gustatory system. The organization of the terminal fields of the chorda tympani (CT), greater superficial petrosal (GSP) and glossopharyngeal (IX) nerves, all of which project to the rostral portion of the nucleus of the solitary tract (NST), change in intact mice when experimental manipulations first occur at adulthood. Therefore, the terminal field organization of these nerves may also be especially plastic in response to nerve injury sustained at adulthood. In our first study, we show that cutting the CT (CTX) in adult mice results in a terminal field size decrease of 66% at 30 and at 60 days post CTX. Since our nerve labeling procedure required cutting the CT before applying an anterograde tracer to the same nerve at 30 or 60 days post CTX, this means that the CT was cut twice. For this procedure, the GSP and IX remained intact. In our second study, we did the same procedure as in the first; however, we also cut and labeled the GSP and IX when the second CTX was done. Surprisingly, we found that the CT terminal field size increased from what we found in the first experiment to be like that in control mice. The change in size occurred within 48 hrs. Thus, the CT terminal field nearly doubled in size when the GSP and IX were also cut with the second CTX. These results indicate that the initial CTX alters (i.e., “conditions”) the environment in the NST such that CT terminal field expands dramatically and rapidly. We are currently examining the effects of multiple CTX procedures at adulthood on the terminal field sizes of the GSP and IX, and potential competitive interactions among the three nerves.

**Disclosures: C. Sun:** A. Employment/Salary (full or part-time); University of Virginia. **D.L. Hill:** A. Employment/Salary (full or part-time); University of Virginia. **A. Erisir:** A. Employment/Salary (full or part-time); University of Virginia.

**Poster**

**PSTR024. Taste**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR024.18/X7

**Topic:** D.04. The Chemical Senses

**Support:** CSULB ORSP

**Title:** Male and female rats categorized by sucralose acceptance display differential intake of ethanol but comparable responses to naltrexone administration

**Authors: K. L. MERKLING**, M. A. BARCELOS, *Y. TREESUKOSOL;
California State Univ. Long Beach, Long Beach, CA

**Abstract:** Individual variability in taste processing contributes to differences in food and fluid intake. Variability in ethanol intake is driven by differences in oral and post-oral cues including association of reward-related signals. When presented water and sucralose in a two-bottle preference test, as sucralose concentration increases some rats drink more sucralose (sucralose preferers; SP) than water and some drink less sucralose (sucralose avoiders; SA). Here, female and male rats categorized for sucralose acceptance were presented 4% ethanol across 4 daily 60-minute test sessions under fluid-restricted conditions. For both female and male groups, SP rats drank significantly more 4% ethanol than their SA counterparts suggesting that SA/SP phenotype is associated with differential intake of ethanol. It has been previously reported that compared to SA rats, SP rats treat sucralose more qualitatively sucrose-like, thus it is possible that SP rats treat ethanol as more sucrose-like than SA rats. Next, 0.01, 0.05, 0.1, 0.5, and 1.0 mg/kg naltrexone, an opioid receptor antagonist, was administered (i.p.) before ethanol presentations. Compared to ethanol intake following saline injections, naltrexone decreased 4% ethanol intake in a dose-dependent manner across all groups. Naltrexone had comparable effects on same-sex SA/SP groups thus sucralose acceptance does not appear to predict responses to an opioid receptor antagonist. Together these findings suggest that SA/SP phenotype is associated with differential ethanol intake which is not likely driven by differences in endogenous opioidergic signaling. It remains possible that differences in the qualitative features of ethanol at least partially contribute to the SA/SP differences in intake

**Disclosures: K.L. Merkling:** None. **M.A. Barcelos:** None. **Y. Treesukosol:** None.

**Poster**

**PSTR024. Taste**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR024.19/X8

**Topic:** D.04. The Chemical Senses

**Support:** R01DC013280
F32DK117671
F32DC018225
Janelia Research Campus Visiting Scientist Program

**Title:** Taste quality and internal state interactions in a feeding sensorimotor circuit

**Authors: *G. R. STERNE**[1], P. K. SHIU[2], S. ENGERT[2], B. J. DICKSON[3], K. SCOTT[2];
[1]Biomed. Genet., Univ. of Rochester Med. Ctr., Rochester, NY; [2]Univ. of California, Berkeley, Berkeley, CA; [3]Queensland Brain Inst., Univ. of Queensland, St Lucia, Australia

**Abstract:** Taste detection and internal state dynamically regulate the decision to begin eating and drinking. To study how neural circuits generate context-dependent ingestion decisions, we combined connectomics with cell-type specific genetic tools to define a gustatory sensorimotor circuit for ingestion initiation in adult *Drosophila melanogaster*. This circuit connects appetitive gustatory sensory neurons to a required motor neuron through three intermediate layers. In hungry and thirsty flies, most neurons in this pathway are necessary and sufficient for proboscis extension, an ingestion initiation behavior. This pathway is largely dedicated to the detection of sugar in hungry flies, but it shifts to encode both sugar and water in thirsty animals. Pathway activity is amplified by hunger and thirst signals that act at select second-order neurons to promote feeding or drinking in a need-dependent manner. In contrast, the ingestion initiation circuit is inhibited by a bitter taste pathway that impinges on premotor neurons, illuminating a local motif that weighs attractive and aversive taste detection to adjust behavioral outcomes. Together, these studies reveal central mechanisms for the integration of external taste detection and internal state to flexibly execute a critical ingestion initiation decision.

**Disclosures: G.R. Sterne:** None. **P.K. Shiu:** None. **S. Engert:** None. **B.J. Dickson:** None. **K. Scott:** None.

**Poster**

**PSTR024. Taste**

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**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR024.20/X9

**Topic:** D.04. The Chemical Senses

**Support:** NIH R01 DC006666
NIH R01 DC007703

**Title:** Basolateral Amygdala and Gustatory Cortex interact bidirectionally during taste processing in rodents

**Authors: *A. MAHMOOD**, J. R. STEINDLER, D. B. KATZ;
Psychology, Brandeis Univ., Waltham, MA

**Abstract:** Activity in Gustatory Cortex (GC) and Basolateral Amygdala (BLA) is known to evolve as a sequence of approximately 3 states during the ~1.5 seconds following tastant delivery onto the tongue of the rat. During these states (early, middle, late), GC activity reflects somatosensation, identity (taste quality), and palatability (hedonic value) respectively, while BLA activity reflects identity and palatability jointly during the middle state. Previous work using symmetric connectivity measures has shown that GC and BLA remain strongly interacting throughout all 3 states, however, the “pattern” of interaction between the regions is different in

every state. To parse this interaction more finely, we characterized the dynamics of the directional influence between BLA and GC using 1) lags in the population state transitions, 2) spike-field coherence, and 3) spectral Granger causality. Furthermore, given previous work which has suggested that GC-to-BLA projecting neurons show patterns of activity distinct from GC *at-large*, we sought to determine whether the directional interaction between the two regions is mediated by distinct subpopulations using Poisson Generalized Linear Modelling of the two populations. We found that: 1) BLA seems to send input to GC during the early epoch (spike-field coherence), however, this input does not seem to significantly impact GC activity (Granger causality), 2) GC and BLA show strong bidirectional connectivity during the middle epoch, and weaker bidirectional interactions during the late epoch, 3) GC-to-BLA and BLA-to-GC "influencing" neurons belong to overlapping populations. These results further support the importance of the BLA-GC interaction during taste processing and invite further investigation into the interaction with other regions in the taste circuit (e.g. gustatory thalamus) during the evolving taste response.

**Disclosures: A. Mahmood:** None. **J.R. Steindler:** None. **D.B. Katz:** None.

**Poster**

**PSTR024. Taste**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR024.21/X10

**Topic:** H.03. Decision Making

**Support:** NIH R01 DC006666
NIH R01 DC007703

**Title:** A novel approach to investigating anticipatory cortical responses to taste associated cues

**Authors: *E. BARASH**;
Brandeis Univ., Waltham, MA

**Abstract:** Survival is inextricably tied to consumption decisions; toxic foods can lead to illness/death, while nutrient-rich foods promote good health. Thus, it is useful to associate cues (e.g., the color of a fruit) with a post-consumption outcome (e.g., eating green, unripe fruit made me sick) to guide approach-avoidance decisions. While cue-driven-association research is common, little research focuses on the decision-making which follows food-cues and leads to food consumption/avoidance. To address this gap, we have developed a novel version of a classic go/no-go task, wherein a rat must trigger a cue and then decide whether to retrieve a reward. This framework allows us to probe the anticipation of food advertised by cues in a multisensory setting designed to separate behaviors elicited by cues from those related to consumption. The task pairs audio-visual cues with palatable (sucrose) and aversive (quinine) taste stimuli. We tested whether rats successfully learn cue-taste associations by determining if they differentially respond to cues corresponding to more preferred tastes. Here, we show rats

tend to approach only palatable stimuli advertised by the cue, suggesting that cue-taste association was learned. Furthermore, the occasional responses to cues advertising aversive taste were long-latency compared to those advertising palatable taste, suggesting uncertainty about a cue's meaning may elicit more careful consideration in making the decision. In the future, this paradigm will be expanded to include electrophysiological interrogation of neural representations of anticipation, decision, and response in GC to understand the neural underpinnings of the differential behavior for different palatability cues.

**Disclosures: E. Barash:** None.

**Poster**

**PSTR025. Visual Cortex: The Function of Neuronal Ensembles and Circuits**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR025.01/X11

**Topic:** D.06. Vision

**Support:** EY029663

**Title:** Neuromodulation by nicotine across a cortical column in V1

**Authors: *V. C. GALVIN**[1], A. A. DISNEY[2];
[1]Neurobio., [2]Dept. of Neurobio., Duke Univ., Durham, NC

**Abstract:** Primary visual cortex (V1) in primates is innervated by an array of neuromodulatory nuclei, and shows distinct expression patterns of modulatory receptors. There is high cholinergic innervation of V1 from the basal forebrain and highly selective β2 subunit-containing nicotinic receptor expression in thalamic axons arriving in layer 4c. In anesthetized primates it has been shown that activating β2-containing nicotinic receptors with nicotine increases responsiveness and lowers the contrast threshold of neurons in layer 4c. How (or whether) these changes in response gain in layer 4c impact propagation of information through visual circuits is unknown. We investigated the effects across a cortical column of activating β2-containing nicotinic receptors in layer 4c. Our results indicate changes to responsiveness and contrast thresholds propagate to both supragranular and infragranular layers within a visual column.

**Disclosures: V.C. Galvin:** None. **A.A. Disney:** None.

**Poster**

**PSTR025. Visual Cortex: The Function of Neuronal Ensembles and Circuits**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR025.02/X12

**Topic:** D.06. Vision

**Support:** MH091844
MH115215
MH111703
EY035068

**Title:** Acetylcholine (ACh) and Norepinephrine (NE) in visual cortex correlate with neural response and goal-directed behavior in nonhuman primates.

**Authors: *F. MUNOZ**[1,4], M. BOMPOLAKI[5], A. DRANOVSKY[2], V. P. FERRERA[3,4]; [1]Neurosci., Columbia Univ., NEW YORK, NY; [2]Psychiatry, [3]Neurosci., Columbia Univ., New York, NY; [4]Zuckerman Mind Brain Behavior Inst., New york, NY; [5]Systems Neuroscience/ Psychiatry, New York State Psychiatric Inst., New York, NY

**Abstract:** Acetylcholine (ACh) and Norepinephrine (NE) agonists and antagonists can modify the responsiveness of neurons in primary visual cortex. However, it has been difficult to measure changes in ACh and/or NE fluctuations and relate these to neural activity and behavior in real-time. A way around these restrictions is to use neurotransmitter-specific genetically encoded sensors whose fluorescence can be measured with fiber photometry. This method enables the monitoring of local neurotransmitter release fluctuations during the execution of behavioral tasks. Here, we describe the use of GRAB-ACh3.0, GRAB-rACh1.7, and GRAB-NE1m to examine the effect of cholinergic and noradrenergic modulation in primary visual cortex (V1) of a rhesus macaque. We used fiber photometry to measure Ach and NE activity with simultaneous single-cell electrophysiology and eye tracking while the animal was engaged in a smooth pursuit task. Our first result indicates a peak at 3Hz (delta wave) in the power spectrum of the ACh fluorescence signal in V1, which correlates with task engagement. A similar peak was found in the frequency spectrum of the LFP signal. In parallel, we found increases in ACh signal correlated with increases in neural firing. A second set of results indicates that ACh and NE signals are correlated in time and frequency during task performance. In particular, ACh and NE exhibit a rise in magnitude at the time of reward in a trial-based analysis. These results have important implications for understanding the role of ACh and NE in the visual cortex during task engagement (attention, arousal, and vigilance). GRAB sensors represent a novel tool that should be useful for investigating the role of modulatory neurotransmitters in processes such as attention and perceptual learning in the nonhuman primate.

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**Poster**

**PSTR025. Visual Cortex: The Function of Neuronal Ensembles and Circuits**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR025.03/X13

**Topic:** D.06. Vision

**Support:** NIH Grant EY05253

**Title:** Binocular receptive field construction in primary visual cortex

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**Abstract:** ON and OFF thalamic afferents from the two eyes converge in primary visual cortex to form binocular receptive fields. Differences in ON-OFF structure and position between the two monocular receptive fields are thought to be important for depth perception. However, quantifying these differences has been challenging because the eyes become misaligned during anesthesia. To address this challenge, we simultaneously recorded from multiple groups of neurons with multielectrode arrays in the anesthetized cat visual cortex, and quantified the eye misalignment in three different axes by calculating the average difference in receptive field position and orientation across 32-64 recording sites. Our results demonstrate that most receptive fields are binocularly matched with exquisite precision across multiple stimulus dimensions including receptive field position, ON-OFF structure, ON-OFF dominant polarity, response time course, response latency, orientation preference, direction preference, orientation selectivity and direction selectivity. The binocular match is most precise for orientation preference ($r=0.94$, $p<0.0001$), but is also significant for orientation selectivity ($r=0.52$, $p<0.0001$), response latency ($r=0.44$, $p<0.0001$), direction preference ($r=0.58$, $p<0.0001$), and direction selectivity ($r=0.51$, $p<0.0001$, $n=549$ receptive fields for all comparisons). After correcting for the eye misalignment, the binocular mismatch for receptive field position is very small and its average is $1/10^{th}$ ($0.53° \pm 0.49°$) of the average receptive field size ($5.9° \pm 1.23°$), with the horizontal-vertical disparity difference being also small but significant ($0.6° \pm 0.51°$ versus $0.46° \pm 0.46°$, $p<0.0001$, $n=586$). Monocular receptive field structures are also highly correlated between the two eyes when measured separately with light or dark stimuli ($r=0.80$, $r=0.82$, $n=586$ and $p<0.0001$ for both), but they are not identical. When the monocular receptive fields are aligned to reach their maximum spatial correlation, the alignment distance is negatively correlated with the maximum spatial correlation ($r=-0.87$, $p<0.0001$, $n=193$ receptive fields with signal to noise $\geq 10$). This relation can be closely replicated by simulating monocular receptive fields with different ON-OFF structures but not different positions (the maximum spatial correlation of identical receptive fields with different positions is always one). Our results provide strong support to phase models of binocular disparity and demonstrate that small but frequent binocular mismatches in ON-OFF structure are needed to efficiently sample local light-dark binocular mismatches in the visual world.

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**Poster**

**PSTR025. Visual Cortex: The Function of Neuronal Ensembles and Circuits**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR025.04/X14

**Topic:** D.06. Vision

**Support:** NIH Grant R01MH128176

**Title:** Adolescent microglial contribution to mature frontovisual circuitry for visual context processing

**Authors: *D. A. RICCI**, A. M. RADER, C. L. WEST, H. S. DALWAI, T. J. SUTTON, J. A. WARGO, G. BASTOS, J. PRAHL, J. M. ROSS, J. P. HAMM;
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**Abstract:** The processing of sensory stimuli in their spatiotemporal and behavioral context is crucial for survival. Stimuli which are unexpected in their current context elicit augmented cortical responses, an effect termed “deviance detection” (DD). In humans, electrophysiological indicators of DD such as the P300 and mismatch negativity (MMN) have been reported to strengthen as adolescence progresses. Looking across adolescence in mice, our lab has previously shown that the refinement of long-range circuitry between prefrontal and sensory regions, marked by increased synchrony, is coupled with the development of DD in visual cortex. Together this suggests that the development of adult-level context processing depends on the adolescent development of cortical circuits. It is known that microglia (MG) support synaptic refinement in neocortex, including synaptic pruning as well as pre-adolescent synaptogenesis, but the significance of MG in adolescent circuit development remains unclear. Furthermore, both DD and microglial function may be impacted in schizophrenia, which onsets during adolescence. Here we investigated the potential role of MG in the shaping of frontovisual circuits responsible for DD during adolescence. In male and female mice, we administered the drug PLX-5622, a CSF1-inhibitor which reversibly eliminates cortical microglia, in mouse chow for one week during pre-adolescence (P28-P35), late-adolescence (P42-P49), or early adulthood (P84-P91), depleting MG by 60-95%. We focused on primary visual cortex (V1) and anterior cingulate area (ACa; a prefrontal region known to project to V1 to support visual context processing), and quantified DD in adulthood via stimulus-evoked responses to a visual oddball paradigm. In this experiment, visual stimuli are presented rapidly, with unexpected “deviant” stimuli interspersed among expected “redundant" stimuli. The MMN, or difference between these responses, indexes DD. We also quantified long-range synchrony between ACa and V1 during the paradigm. To confirm PLX-5622’s depletion of MG, we utilize a MG-GFP mouse line to quantify MG in ACa and V1 for each age group. Our results indicate that depletion of MG in adolescence and early adulthood leads to altered long-range synchrony, although DD was present in all mice. The data are consistent with findings that MG dysfunction in adolescence alters normal cognitive maturation. These findings have implications for understanding neuropsychiatric diseases like schizophrenia, which display deficits in context processing, alterations in immune function, and onset during late adolescence.

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**Poster**

**PSTR025. Visual Cortex: The Function of Neuronal Ensembles and Circuits**

**Location:** WCC Halls A-C

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**Topic:** D.06. Vision

**Support:** 2T32EY007135-26
R01EY027402

**Title:** Interocular normalization across the V1 laminar microcircuit

**Authors: *B. MITCHELL**, B. CARLSON, A. MAIER;
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**Abstract:** The primary visual cortex (V1) in primates integrates visual information from both eyes to generate a unified binocular output. Although the precise neuronal mechanisms governing this binocular combination remain incompletely understood, it can be described as a process of divisive normalization operating between the eyes (i.e., interocular normalization) within *binocular* neurons. However, the extent to which interocular normalization is expressed across the laminar microcircuitry of V1 remains unexplored. In this study, our objective was to investigate the spatial distribution of interocular normalization in V1. To accomplish this, we employed linear microelectrode arrays to record spiking activity across all six cortical layers of V1 while monkeys passively viewed grating stimuli. These gratings were either shown to one eye (monocular), to both eyes with equal contrast levels (binocular balanced), or to both eyes with different contrast levels (binocular imbalanced). Subsequently, we applied both an interocular normalization model and a model that linearly sums contrast between the eyes to fit the binocular data. By comparing the performance of these models, we derived an index of normalization strength as a function of cortical depth. Our findings revealed that neurons located in layers 2/3 and 5/6 of V1 exhibited the highest degree of normalization, while neurons in the granular input layer 4C displayed the weakest normalization and the most linear summation of contrast between the two eyes. These results offer insights into the laminar specificity of normalization processes within the early visual cortex, providing further understanding of the circuit mechanisms underlying binocular integration.

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**Poster**

**PSTR025. Visual Cortex: The Function of Neuronal Ensembles and Circuits**

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**Topic:** D.06. Vision

**Support:** NIH Grant K99EY033974 (BRAIN Initiative)

**Title:** Novel Neuronal Ensembles Emerge During Visual Learning

**Authors: *A. AKROUH**, J. PEREZ-ORTEGA, R. YUSTE;
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**Abstract:** The brain undergoes extensive synaptic plasticity and circuit refinement during learning and development. Understanding how neuronal connections and activity are adaptively remodeled to accommodate a changing world remains an outstanding question in neuroscience research. Recent technological innovations provide unprecedented access to address this. Here, we investigated the circuit mechanisms that reconfigure neuronal ensembles in mouse primary visual cortex (V1) during perceptual learning. Using volumetric two-photon (2P) calcium imaging, we longitudinally tracked the activity of thousands of neurons in V1, with single-cell resolution, throughout a visual learning Go/No-Go paradigm. We find that novel cortical ensembles emerge in expert mice that encode for specific phases of the behavioral task. In response to visual task demands, cortical ensembles shift their response properties to "give" salience to relevant features in visual space. Our findings will provide new insights to the circuit mechanisms that establish homeostasis in neuronal activity while simultaneously yielding sufficient flexibility to accommodate learning. Future experiments will combine 2P optogenetics and a spatial light modulator (SLM) to holographically activate and inactivate specific functionally and/or molecularly defined subpopulations of neurons. These experiments will thus probe the interactions between expert cortical ensembles to causally uncover the circuit elements that underlie cortical plasticity. As many neuropathological states arise when this balance is disrupted, a greater understanding of physiological circuit function will contribute to the development of novel therapeutics to treat disorders of the nervous system.

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**PSTR025. Visual Cortex: The Function of Neuronal Ensembles and Circuits**

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**Topic:** D.06. Vision

**Support:** IBS-R015-D1
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**Title:** Layer-specific processing of apparent motion perception in macaque primary visual cortex

**Authors: *H. KIM**[1,2], J. LEE[1,2,3];
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**Abstract:** Primate visual cortical areas are organized in hierarchical manner and interconnected by feedforward and feedback pathways. These pathways serve distinct roles in processing of visual information, contributing to various aspects of cognition and perception. However, the precise nature of the interactions between feedforward and feedback processing in the visual cortex remains uncertain. To address this, we exploited the phenomenon of apparent motion-induced masking. Apparent motion (AM) is the illusory motion perception induced between two stimuli presented alternately at separate locations, and several behavioral studies reported that this internal representation impairs the detection of stimuli with visual features similar to that of the interpolation between the AM-inducing stimuli (Yantis and Nakama 1998; Hidaka et al., 2011; Chong et al., 2014). Since several types of illusory perception including AM are thought to be driven by feedback processing, this masking of feedforward sensory input could be caused by presumed feedback processing. We trained two rhesus monkeys to report the absence or location of a visual target flashed within alternating inducers by making a saccade to one of three decision dots while recording from primary visual cortex neurons. Gabor wavelets with 8 orientations separated by 22.5 degrees were used as target stimuli, with two contrast levels (12% and 32%). The inducer's orientation and contrast remained consistent at 90 degrees and 100%, respectively. Both monkeys exhibited high performance above 80%. However, detection accuracy was reduced when the targets had orientations similar to the inducers. As ascending feedforward projections and descending feedback projections can be distinguished based on laminar differences in projection patterns, all cortical layers that received inputs from different regions were simultaneously recorded using laminar electrodes. The CSD calculation was utilized to approximate the laminar boundaries. In the granular layer, when the orientation of the target was close to that of the inducer, the neural response to the target was reduced compared to the case where the orientations were dissimilar. The most significant reduction in response occurred when the target and inducer orientations matched. This suppression of activity in the granular layer is consistent with previous studies of computational models (Van Humbeeck et al., 2016) and human fMRI (Shen et al., 2020). However, the orientation of target did not affect the neural response to the target in the supragranular layer. Our findings suggest that the effect of AM manifests differently depending on the specific cortical layer.

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

**Poster**

**PSTR025. Visual Cortex: The Function of Neuronal Ensembles and Circuits**

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**Title:** Layer-specific plasticity of feedforward and contextual neuronal populations in mouse visual cortex

**Authors:** K. SEIGNETTE[1], P. PAPALE[2], L. DE KRAKER[1], P. NEERING[1], M. VAN DER AA[1], B. HOBO[3], C. VAN DER TOGT[1], M. W. SELF[2], ***C. N. LEVELT**[4];
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**Abstract:** Our brains are extremely efficient in interpreting and responding to constant streams of highly complex sensory information. One increasingly influential concept of how the brain achieves this is predictive coding. It views the brain as a hypothesis-testing machine that compares an internal model of the environment with sensory inputs it receives. It tries to minimize the difference between the two by calculating errors in the prediction and using these to update the internal model. This requires neurons that encode the internal representation, and those that encode prediction errors. Identifying the cell types that encode prediction errors or internal representations has been extremely challenging, mainly because responses to visual inputs and predictions are strongly intertwined. Here, we used occlusion of natural visual scenes to separate visual and predictive responses across layer 2/3 (L23) and layer 5 (L5) in mouse primary visual cortex (V1) and study the effect of visual training on these responses. We recorded activity from L23 or L5 neurons in mouse V1 using chronic two-photon and widefield calcium imaging in awake mice. We mapped population- and single cell receptive fields (RFs) and then presented six (partially) occluded and full natural scenes. To study the effects of learning, we trained mice to detect a subset of these natural scenes in full condition while leaving the others out. This resulted in familiarity with some, but not other images. Single-cell responses to full and occluded scenes were recorded again after training. Finally, we used a convolutional neural network (CNN) to model visual responses and most exciting inputs (MEIs) to compare visual properties between populations of neurons. For all analyses we only included neurons that had their RFs in the occluded region of the images. L23 neurons responded exclusively to either the full images or the occluded images. Perceptual learning decreased responses to familiar images but increased those to novel images. In L5, responses to the full images dominated and those to novel images enhanced even more after training. Responses to occluded stimuli were weaker and did not change with experience. Finally, decoding image identity from occluded responses was possible both in L23 and L5 and slightly increased after training. Our results show that different subsets of pyramidal neurons in L23 and L5 respond selectively to full and occluded images and are strongly influenced by experience. We will discuss these results in the framework of predictive coding.

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**Poster**

**PSTR025. Visual Cortex: The Function of Neuronal Ensembles and Circuits**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR025.09/X19

**Topic:** D.06. Vision

**Support:** NEI R00EY028964

**Title:** Visual sequence encoding in mouse anterior cingulate cortex: local mechanisms and long-range circuits

**Authors: *A. MALCI**[1], M. S. SIDOROV[1,2];
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**Abstract:** The anterior cingulate cortex (ACC) is a prefrontal brain area implicated in a broad range of functions including cognitive control, emotion regulation and pain perception in mice. Also, ACC receives direct input from the visual cortex (VIS) and responds to visual stimuli. Our previous work demonstrated that patterned visual experience drives plasticity in mouse ACC. Here, we seek to understand the circuits responsible for visual encoding and experience-dependent plasticity in mouse ACC. We investigate anatomical connectivity of ACC and VIS by using anterograde and retrograde viral tracing tools and immunohistochemistry. We show that ACC receives monosynaptic inputs from both primary visual cortex (V1) and medial secondary visual cortex (V2M), with a stronger input coming from V2M. Finding of anatomical inputs originating from visual areas becomes our motivation to explore functional anatomy of VIS-ACC projections. For this, we perform chemogenetic manipulation of VIS-ACC projections and combine this approach with in vivo visually evoked local field potential (VEP) recordings in awake mice to assess the functional role of VIS-ACC projections in visual information processing. We study sequence plasticity which is a particular type of experience-dependent plasticity and is established by repeated presentations of a familiar visual sequence. We confirm that sequence plasticity in ACC and V1 is driven by an extended presentation of visual sequences which helps us to monitor temporal changes in VEPs across four days. In addition, we investigate the potential consequences of chemogenetic inhibition of V1 or V2M during stimulus presentation on sequence plasticity in ACC. With ongoing in vivo studies, we aim to better understand the importance of VIS-ACC projections for visual input encoding and also sequence plasticity. Our anatomical and functional characterization of VIS-ACC circuitry in wild-type mice will also support our parallel studies focusing on how sequence plasticity is interrupted in a mouse model of a neurodevelopmental disorder namely Angelman syndrome (AS).

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**Poster**

**PSTR025. Visual Cortex: The Function of Neuronal Ensembles and Circuits**

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**Title:** Responses of different neuron types to patterned sensory stimulation in a bio-realistic model of mouse primary visual cortex

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**Abstract:** Patterned sensory stimulation (PSS) has gained interest as a non-invasive technique for manipulating the activity and states of the brain (Adaikkan & Tsai, 2020). PSS in the gamma range (centered at 40 Hz) causes neural entrainment to rhythmic oscillations and elicits behavioral and cognitive changes. However, the underlying mechanism remains unclear. Here we examine the responses of diverse types of cortical neurons to PSS at different frequencies using a data-driven bio-realistic model of the mouse primary visual cortex (V1). The model is built based on a previously published model of mouse V1 (Billeh et al., 2020). It consists of nearly 300,000 neurons from 19 major cell classes, including layer-specific groups of excitatory neurons, and parvalbumin, somatostatin, and VIP interneurons, with realistic geometry, neuronal densities, and connectivity. Neurons are simulated using generalized leaky integrate and fire point-neuron models constrained by experimental measurements. The model enables simulations of arbitrary visual stimuli and exhibits good agreement with data from large-scale extracellular electrophysiology recordings in vivo.
To simulate the visual PSS, we present the model with a full-field square wave light flicker at different frequencies (5 Hz, 8 Hz, 40 Hz, and 40 Hz with random intervals from a Poisson process). Power spectral analysis using the population activity of each neuron type shows that most neuron types exhibit rhythmicity at the stimulus frequency for the 5, 8, and 40 Hz stimuli. We also quantify the entrainment of each individual neuron by computing the pairwise phase consistency of their spikes to the stimulus cycle. In order to examine the contribution of each inhibitory cell type, we systematically block the synapses from each of the three interneuron cell types. We describe how blocking synapses from each type of inhibitory neuron affects the activity and entrainment of other neuron types, with specific and distinct contributions from parvalbumin, somatostatin, and VIP populations. Together, these results provide insights into the roles of cell types and circuit properties mediating the effects of PSS and can guide focused experimentation in the future.
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**Poster**

**PSTR025. Visual Cortex: The Function of Neuronal Ensembles and Circuits**

**Location:** WCC Halls A-C

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**Title:** Input filtering via attenuation in visual cortical networks measured with single-cell stimulation

**Authors: *P. LAFOSSE**[1], Z. ZHOU[2], V. SCOTT[2], Y. DENG[2], M. HISTED[2];
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**Abstract:** The relationship between neurons' input and spiking output is a fundamental aspect of brain computation. In silico work confirms that the shape of input-output functions is important to network operation, impacting both the learning efficiency and performance of artificial neural networks. In the brain, prior work in vitro and in anesthetized animals suggests that neurons' transfer functions can vary as a function of network activity (Anderson et al., 2000; Hansel and van Vreeswijk, 2002; Miller and Troyer, 2002; Carandini, 2004). However, the shapes of *in vivo* transfer functions, and the operating point of neurons on these curves during the awake state, are not well known. Here, we measure input-output functions in awake mice using two-photon stimulation of single neurons at different levels of activity, and find that neurons hover near the top of a prominent supralinearity in their transfer function. This supralinearity, generated by ongoing intracortical activity, means that as cells are suppressed, their responses to input are dramatically decreased. Thus, our results describe a cortical mechanism by which inputs can be attenuated: attenuation-by-suppression.
To directly measure the shapes of input-output functions, we study excitatory neurons (N=367) in primary visual cortex (V1) of awake mice. We measure cells' activity with two-photon calcium imaging during both spontaneous conditions - that is, in the absence of visual stimuli - and during vision. We find that as cells increase their firing rate due to visual input, responses to a constant optogenetic input remain largely unchanged (i.e. linear response; N=70; p=0.3, K-S test), before eventually saturating. On the other hand, as cells are suppressed below their spontaneous activity levels, optogenetic responses are reduced dramatically (N=101; p=10^-7). Thus, the average input-output function of V1 neurons is characterized by a supralinear regime followed by a substantial linear regime before response saturation. Moreover, cells operate near the transition point from nonlinear to linear during spontaneous activity levels. Taken together, this work suggests that ongoing activity in cortical networks can enhance sensory processing of external stimuli by selectively filtering extraneous features of sensory input via attenuation in suppressed cells (Chen et al., 2022; Azadi et al., 2023).

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**Poster**

**PSTR025. Visual Cortex: The Function of Neuronal Ensembles and Circuits**

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**Topic:** D.06. Vision

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**Title:** Selective amplification of sequences of neural activity by recurrent circuits of visual cortex.

**Authors: *C. DEVEAU**[1], Z. ZHOU[2], P. LAFOSSE[3], Y. DENG[2], S. MIRBAGHERI[4], N. A. STEINMETZ[4], M. HISTED[2];
[1]Brown Univ. - NIH, Bethesda, MD; [2]NIH / NIMH, Bethesda, MD; [3]NIMH/UMD Col. Park, North Bethesda, MD; [4]Univ. of Washington, Seattle, WA

**Abstract:** As we interact with the world, we receive streams of sensory input that change over time. How do sensory cortical networks process such dynamic input? In many artificial networks, recurrent connections between nearby neurons can produce selective responses to input based on temporal context. To understand how cortical neurons' activity interacts across time, we use two-photon stimulation to give input to groups of neurons at single-cell resolution. Using this approach, we test and confirm a hypothesis for the function of recurrent connections in primary visual cortex (V1): that recurrent connections amplify sequences of input patterns that correspond to natural visual inputs. In V1, simple stimuli like gratings generate responses in numerous cells, while dynamic inputs like natural movies generate strong and sparse responses. We first test if the context of a dynamic visual movie can amplify a relevant input pattern. We image the response to a single frame of a natural movie, then play back the evoked response pattern at the correct time point in the movie and find that this input is amplified in the correct natural dynamic context compared to when presented during a control natural movie that is mismatched (avg. resp. matched 36±1.8% df/f, mismatched 26±1.5% df/f). The response to a pattern in the correct movie context is also sparser (pop. sparsity matched = 0.88; mismatched = 0.71). We then use sequences of two-photon stimulation alone, without visual input, to identify how this sequence amplification can occur. We find that a single input pattern generates suppression in some off-target (non-stimulated) neurons and this suppression is sustained over several later movie frames (FWHM=225±1ms). We also find that suppression leads to attenuated response to input. Taken together, this explains how some sequences can be amplified by the cortex: local, cell-specific suppressive interactions allow the response to one movie frame to influence responses to later frames. We test this mechanism by generating two-photon pattern sequences predicted to be amplified, and find that indeed such patterns produce both stronger and sparser responses compared to patterns predicted to be suppressed. In sum, we propose that sequence amplification is a general mechanism by which cortical networks filter dynamic inputs, boosting sequences of input relevant to natural sensation and behavior.

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**Title:** Neuronal Sequences in the Human Cortex Encode Information of Visual Images

**Authors: *W. XIE**, J. WITTIG, Jr, S. JACKSON, S. INATI, K. ZAGHLOUL;
NIH, Bethesda, MD

**Abstract:** The human brain performs unparalleled complex computations while consuming only a few watts of energy. In contrast, advanced artificial intelligence can require megawatts of electricity, equivalent to powering thousands of homes in a small town, to learn basic cognitive operations like image classification. How does the human brain achieve such computational efficiency? One possibility is that the human brain employs multiple neural coding schemes to efficiently represent information. For example, in addition to population spike rate coding, differences in the precise timing of spiking activity can create unique sequences for efficient information representation. However, despite evidence from animal models, the contribution of neuronal sequences to human cognition remains poorly understood. It is unclear whether neuronal sequences serve a general information coding function and whether they are redundant with population spike rate coding. To address these questions, we directly recorded 2,110 single units from 8 participants using micro-electrode arrays in the anterior temporal lobe during a visual categorization task with various taxonomic categories (e.g., PEOPLE, ANIMAL, PLACE, OBJECT). Our findings confirm that population spike rate can differentiate stimulus information from different visual categories. More importantly, population spiking activity tends to organize in bursts, with units spiking closely in time within a range of 50-150 ms. Within each burst, the precise spiking timing of activated units varies, creating unique spiking sequences for stimuli from individual categories. Formal analyses show that the stimulus information conveyed by the temporal order of a unit's spike timing and the number of spikes within a burst are separable and non-redundant. Furthermore, units contributing more to population rate coding tend to spike earlier in a burst sequence. Collectively, our data suggest that the human brain may employ multiple neural codes to synergistically and efficiently represent higher-level visual information.

**Disclosures:** **W. Xie:** None. **J. Wittig:** None. **S. Jackson:** None. **S. Inati:** None. **K. Zaghloul:** None.

**Poster**

**PSTR025. Visual Cortex: The Function of Neuronal Ensembles and Circuits**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR025.14/X24

**Topic:** D.06. Vision

**Title:** Modeling effects of stimulus novelty on cortical circuitry

**Authors: *S. ITO**[1], A. PIET[2], C. BENNETT[2], S. DURAND[2], H. BELSKI[2], M. GARRETT[2], S. R. OLSEN[2], A. ARKHIPOV[1];
[2]Allen Inst. for Neural Dynamics, [1]Allen Inst., Seattle, WA

**Abstract:** Understanding how the brain adapts to novel stimuli is crucial for comprehending animal behavior in realistic environments. Recent research demonstrates that stimulus novelty alters cortical dynamics in a cell subclass-specific manner (Garrett, bioRxiv, 2023). In this study, we utilized the Allen Institute's Visual Behavior dataset (http://portal.brain-map.org/explore/circuits/visual-behavior-neuropixels) to investigate how novel stimuli reshape cell-type specific dynamics in layer 2/3 of the mouse primary visual cortex. We used the Stabilized Supralinear Network (SSN) model to capture the population-level dynamics of excitatory population and three populations of inhibitory subclasses—parvalbumin (PV) somatostatin (SST), and vasoactive intestinal peptide (VIP)—during the image presentations and omissions in familiar and novel contexts. We constrained the model parameters—the connection weights—with results from multi-patch synaptic physiology and electron microscopy (EM) datasets (https://portal.brain-map.org/explore/connectivity/synaptic-physiology, https://www.microns-explorer.org/cortical-mm3).With a systematic model optimization strategy, we found many (~30,000) sets of parameters that successfully reproduced the firing rate traces of all subclasses from *in vivo* Neuropixels recordings, including complex shifts in VIP population activity between the familiar and novel context. By analyzing changes in the sets of model parameters between familiar and novel contexts, we identified that connections from excitatory cells and PV cells were important for distinguishing the two stimulus contexts. Specifically, we found that the transition from the familiar context to the novel context is marked by inhibition of the excitatory population and excitation of the PV and SST populations. Furthermore, our results highlight the unique contribution of connections to the VIP population in differentiating temporal data segments such as stimulus and omission periods. Our study blends multiple large-scale datasets—*in vivo* Neuropixels recordings, EM connectomics, and multipatch synaptic physiology—to uncover a possible neural mechanism underlying cortical responses to familiar and novel stimuli. Our model generates testable hypotheses for future experiments that can uncover how cortical circuits dynamically respond to changing environmental and cognitive demands.

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**Poster**

**PSTR025. Visual Cortex: The Function of Neuronal Ensembles and Circuits**

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**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

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**Topic:** D.06. Vision

**Support:** NIH U24NS113646
NIH R00MH116100
Vanderbilt Brain Institute Faculty Fellow Award
Openscope Program

**Title:** Global and local oddball detection across the mouse visual cortical hierarchy

**Authors: *J. A. WESTERBERG**[1], S. DURAND[2], A. BAWANY[2], H. CABASCO[2], H. LOEFFLER[2], H. BELSKI[2], B. HARDCASTLE[2], S. OLSEN[2], J. LECOQ[2], A. MAIER[3], A. BASTOS[3];
[1]Netherlands Inst. for Neurosci., Amsterdam, Netherlands; [2]Allen Inst., Seattle, WA; [3]Vanderbilt Univ., Nashville, TN

**Abstract:** Recent years have seen significant progress in our understanding of the neural basis of perception and prediction by studying sophisticated variants of oddball tasks. Specifically, by differentiating between so-called local (1st order) versus global (2nd order) oddballs, it has become possible to dissociate automatic mechanisms of prediction from context-driven forms of predictive processing. Cortical responses to local oddballs occur reflexively, even under deep anesthesia. Cortical responses to global oddballs, on the other hand, require conscious processing. However, little is known about the neural circuitry supporting these two types of stimuli. Prior work in mice suggests that V1 reflects the same response patterns found in other species (sequence learning and local oddball detection). Yet, inter-areal, laminar-resolved data are needed to localize the origins and feedforward vs. feedback propagation of these effects, and the global oddball paradigm has not yet been studied in this way. We performed simultaneous NeuroPixels recordings spanning 6 areas along the mouse visual cortical hierarchy while animals viewed sequences with either predictable local oddballs or unpredictable global oddballs. At the population level, aggregating thousands of single units across recorded areas, we found a robust local oddball detection signal and a weaker, but reliable, global oddball detection signal. Analyses with respect to cortical area revealed signatures of both oddball detections could be seen spanning the hierarchy, global oddball detections were seemingly not limited to higher-order cortex. These findings confirm that signatures of local and, more surprisingly, global oddballs can be found at the level of neuronal spiking and also demonstrate that these selective signals exist at the earliest stages in sensory cortical processing.

**Disclosures: J.A. Westerberg:** None. **S. Durand:** None. **A. Bawany:** None. **H. Cabasco:** None. **H. Loeffler:** None. **H. Belski:** None. **B. Hardcastle:** None. **S. Olsen:** None. **J. Lecoq:** None. **A. Maier:** None. **A. Bastos:** None.

**Poster**

**PSTR025. Visual Cortex: The Function of Neuronal Ensembles and Circuits**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR025.16/Y1

**Topic:** D.06. Vision

**Support:** (U24 NS113646

**Title:** Openscope: a platform for high-throughput and reproducible neurophysiology open to external scientists to test impactful theories of brain function

**Authors: *J. LECOQ**, S. DURAND, S. CALDEJON, A. BAWANY, C. KISELYCZNYK, C. FARRELL, P. A. GROBLEWSKI, N. ORLOVA, S. M. SEID, X. WAUGHMAN, A. WILLIFORD, J. SWAPP, C. PEENE, B. HARDCASTLE, H. CABASCO, H. LOEFFLER, H. BELSKI, S. OLSEN, C. KOCH;
Allen Inst., Seattle, WA

**Abstract:** The OpenScope platform, an evolution of the Allen Institute's Allen Brain Observatory, offers an innovative model for neuroscience research. Established as a public observatory of the mind, OpenScope provides the global scientific community with free access to a high-quality, standardized neuroscientific experimental platfom, fostering a collaborative environment analogous to astronomical observatories that survey the night sky.
OpenScope harnesses cutting-edge Neuropixels recordings and two-photon calcium imaging techniques in conjunction with advanced behavioral training methods. These strategies facilitate brain surgery, animal training, neuronal recordings, and brain reconstruction, embodying a comprehensive data collection pipeline. Previous data collections under similar conditions have resulted in the public release of calcium imaging data from ~60,000 cells from 221 running mice and Neuropixels electrophysiology recordings from ~100,000 cells from 100 mice. The richness of these datasets has enabled sophisticated analyses of neural activity, fueling the generation of novel hypotheses regarding brain function.
Projects are accepted on a yearly cycle, where they are reviewed for feasibility and scientific merit by a panel of leading experts, including the OpenScope Scientific Steering Group. This process includes an initial screening of Letters Of Intent (LOI) by internal Allen Institute reviewers, followed by the submission and review of full, six-page proposals by the top-scoring applicants.
Data produced are curated, standardized, and shared via Neurodata Without Borders (NWB) files in the cloud following a one-year embargo, eliminating the need to disseminate large files and facilitating efficient meta-analysis across experiments. This platform fosters an atmosphere of open scientific discourse, facilitating selected teams to analyze and submit their outcomes to bioRxiv and peer-reviewed journals.
Through the conduct of selected experiments and subsequent data release, OpenScope continues to catalyze progress in neuroscience. This platform builds a supportive community through a yearly workshop and data portal, enabling past, present, and potential future awardees to communicate their research projects effectively. By implementing the observatory model,

reducing variability across experiments, and lowering barriers to idea validation, OpenScope accelerates progress toward an integrated understanding of neural circuits.

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**Poster**

**PSTR025. Visual Cortex: The Function of Neuronal Ensembles and Circuits**

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Western Academy of Advanced Research (L.M.)

**Title:** A new method for analyzing spatiotemporal patterns in neural activity relates repeating motifs in marmoset area MT to behavior in a challenging visual detection task

**Authors: *A. N. BUSCH**[1], Z. W. DAVIS[2], J. H. REYNOLDS[3], L. E. MULLER[4];
[1]Univ. of Western Ontario, London, ON, Canada; [2]SNL-R, Salk Inst., La Jolla, CA; [3]SNL-R, Salk Inst., Del Mar, CA; [4]Dept. of Mathematics, Western Univ., London, ON, Canada

**Abstract:** Recent technological advances have dramatically increased the number of sites that can be simultaneously recorded in the cortex of awake, behaving animals. It is now possible to study how neural activity evolves across hundreds to thousands of recording sites within a single cortical area, or across distributed networks spanning multiple regions, at the same time. These large-scale data sets invite new and exciting research questions, but they also present new challenges. Specifically, there is a need for new signal processing methods designed to analyze the neural activity patterns that dynamically evolve across these large-scale recordings, and to relate these spatiotemporal patterns to behavior. To address this challenge, we introduce a method for detecting repeated spatiotemporal patterns in neural activity. When a specific, distributed pattern of activity occurs more often than expected by chance, we call this a "spatiotemporal motif". Using a recently introduced technique to characterize the phase of

fluctuating, broadband signals, we represent spatiotemporal patterns of neural activity as patterns of phases. We then introduce an index to quantify the similarity between these phase patterns, which allows us to define a rigorous mathematical procedure to measure the degree of similarity between "movies" of neural activity. The relationships of similarity between patterns are then collected into a network that characterizes how spatiotemporal activity evolves across an entire recording session. Using techniques from spectral graph theory, we can then analyze this network and find "communities" of similar spatiotemporal patterns, in an unsupervised manner. Applying this technique to spontaneous activity during Utah array recordings in marmoset area MT, we find specific spatiotemporal motifs indeed repeat more often than chance in these data. We hypothesized that these motifs may be related to the clustered, feature-specific connectivity in MT. Consistent with this hypothesis, identified motifs are associated with upregulation of ongoing undriven activity among neurons with shared feature preference and changes in perceptual sensitivity in marmosets performing a challenging visual detection task. These results demonstrate that this method can find meaningful spatiotemporal patterns of activity in neural recordings that can then be directly related to behavior.

**Disclosures:** **A.N. Busch:** None. **Z.W. Davis:** None. **J.H. Reynolds:** None. **L.E. Muller:** None.

**Poster**

**PSTR025. Visual Cortex: The Function of Neuronal Ensembles and Circuits**

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**Topic:** D.06. Vision

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**Title:** Spatiotemporal motifs coordinate intrinsic fluctuations among like-tuned populations impacting feature-dependent perceptual sensitivity

**Authors: *Z. W. DAVIS**[1], A. BUSCH[3], L. MULLER[4], J. H. REYNOLDS[2];
[2]SNL-R, [1]Salk Inst., La Jolla, CA; [3]Univ. of Western Ontario, London, ON, Canada; [4]Western Univ., London, ON, Canada

**Abstract:** A central question in neuroscience is what are the sources and functional consequences of variability in the activity of cortical neurons. As a simple example, identical presentations of a visual stimulus yield variable responses and this variability is correlated with perceptual choices made in visual tasks. One source of variance is intrinsic fluctuations in synaptic activity that vary from moment-to-moment. Rather than synchronous or statistically independent, these fluctuations often have organized spatiotemporal structure across neuronal populations, for example in the form of traveling waves (Davis*, Muller* et al. Nature 2020).

We have developed a spiking network model in which these waves reflect patterns of spiking activity as they traverse long range horizontal projections (Davis*, Benigno*, et al. Nat. Comm. 2021). Anatomical studies suggest that these horizontal projections, to some extent, preferentially connect neurons that share tuning preference. When we incorporate these long range feature-selective connections into our model, we find that some spatiotemporal patterns in the network tend to repeat. We refer to these as "motifs". To test the model predictions in vivo, we have reanalyzed data that we previously collected using Utah arrays in Area MT of marmosets as they performed a challenging visual detection task. Consistent with the model, we find evidence for motifs in ongoing intrinsic activity. Further, we find that motif patterns are associated with the preferential modulation of spontaneous spiking among neurons with similar tuning preferences. The coincidence of a motif with tuning preference for the direction of motion of the target in the detection task predicts increases in evoked gain and improved detection performance. These results are consistent with the view that the spatiotemporally structured activity in a cortical area is shaped by the anatomical organization of horizontal fibers. We speculate that these horizontal fibers have come to reflect statistical regularities in the visual environment and that they may play a role in supporting internal representations of the external world based on how they modify sensory input.

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**Poster**

**PSTR025. Visual Cortex: The Function of Neuronal Ensembles and Circuits**

**Location:** WCC Halls A-C

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**Topic:** D.06. Vision

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**Title:** The Phase Coherence in Alpha and Beta Frequency Bands is Associated with the Modulations of Target Visibility in Visual Masking

**Authors: *I. AKDOGAN**[1,2], H. KAFALIGONUL[1,2];
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**Abstract:** Neural oscillatory phase synchronization can provide deeper insights into the temporal dynamics of visual processing. Previous studies have shown that phase coherence (or phase-locking) in particular frequency bands can reflect behavioral performance in visual detection (Busch et al., 2009), discrimination (Drewes & VanRullen, 2011), and visual awareness (Mathewson et al., 2009). Notably, Fries (2005) proposed that the communication between different groups of neurons might be subserved effectively through phase coherence. However, the exact relationship between rhythmic oscillations and corresponding sensory processing

requires further investigation (VanRullen, 2016). In this study, we hypothesized that changes in phase coherence might be associated with the variability in visual discrimination ability in backward masking. We have used the EEG data of two backward masking experiments in which the target visibility was manipulated by the contrast ratio/magnitude or polarity of the mask across different onset timing conditions (SOAs) while the observers performed a contour discrimination task. The behavioral results of the contrast ratio (n=16) and polarity (n=14) experiments overall indicated typical U-shaped masking functions in which the target visibility was strongly suppressed at the intermediate SOAs (around 50-80 ms). However, in the opposite mask polarity condition, the masking function was a monotonic increasing function such that the target visibility was strongly suppressed at an SOA of 10 ms. We employed time-frequency analyses with cluster-based permutation tests (Maris & Oostenveld, 2007) on the EEG data to assess inter-trial phase coherence across these different masking conditions. The analyses revealed significant modulations in the alpha and early beta (around 9-20 Hz) frequency bands. Furthermore, in the intermediate SOAs, when visibility suppression occurred in both the contrast ratio and same polarity conditions, the target-locked phase synchronization was notably increased after the mask presentation, and this synchronization was further enhanced with the masking amount. Also, in the early SOA of the opposite polarity condition, target-locked phase synchronization was disrupted by the presence of the mask. Remarkably, we observed modulations in the phase synchronizations consistent with the changes in behavioral performance values associated with perceived target visibility. Based on previous theoretical studies on visual masking, these observed changes in phase coherence values may be attributed to inhibitory interactions between (and within) neural pathways.

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**Poster**

**PSTR026. Functional Architecture of the Visual System**

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**Program #/Poster #:** PSTR026.01/Y5

**Topic:** D.06. Vision

**Support:** EY013574

**Title:** Impact of type 3 oculocutaneous albinism in a non-human primate on the functional organization of the visual system

**Authors: *P. AUDURIER**[1], L. M. RENNER[1], S. M. PETERSON[2], N. M. HOQUE[3], M. NEURINGER[1], R. M. FRIEDMAN[1];
[1]Div. of Neurosci., [2]Div. of Genet., OREGON NATIONAL PRIMATE RESEARCH CENTER, Beaverton, OR; [3]Lewis & Clark Col., Portland, OR

**Abstract:** Albinism is a rare genetic pathology characterized by abnormal melanin synthesis, affecting eyes, hair and skin pigmentation. Albinism has profound effects on the development of

the human visual system, including foveal hypoplasia and aberrant crossing of optic nerve through the optic chiasm, resulting in functional deficits such as reduced visual acuity, strabismus, nystagmus and amblyopia. In particular, excessive crossing of contralateral optic nerve fibers can lead to an aberrant representation of the ipsilateral visual field and abnormal retinotopic representation in V1. While albinism has been studied in a variety of animal models, only a few studies have involved non-human primates. Here we describe the impact of a genetic mutation in the tyrosinase-related protein 1 (TYRP1) gene on the morphology of the eye and the optic chiasm, and on the functional organization of primary visual cortical areas, in a rhesus macaque with a golden/blond hair coat phenotype. In humans, mutations in TRYP1 lead to a phenotype of oculocutaneous albinism type 3 (OCA3) that is associated with mild visual abnormalities. In this case, color retinal fundus images and optical coherence tomography (OCT) scans revealed reduced ocular pigmentation and foveal hypoplasia. MRI also revealed a smaller optic chiasm when compared with age and sex matched controls. Intrinsic optical imaging (IOI) did not reveal functional abnormalities in the basic organization of striate cortex with respect to ocular dominance columns (ODCs), orientation pinwheels and color blobs. Anticipated abnormalities in retinotopy were absent, especially along the vertical meridian (V1 and V2 border). However, we did observe cortical magnification asymmetries in the contralateral vs. ipsilateral inputs. Unexpectedly, the cortical magnification factor (mapping of visual eccentricity on cortex) and the population response (size of cortical activity elicited by a visual stimulus) were smaller for the contralateral than ipsilateral eye for vertical square wave gratings. Given evidence for aberrant projections from the two eyes in OCA3, we propose that differences in projections from the two eyes into their respective ODCs could account for this difference. Investigations of an OCA3 rhesus model will lead to a better understanding of the neural mechanisms underlying the visual abnormalities present in the many albinism phenotypes.

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**Poster**

**PSTR026. Functional Architecture of the Visual System**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR026.02/Y6

**Topic:** D.06. Vision

**Title:** A model for the development of chromatic border selectivity in macaque primary visual cortex

**Authors:** M. SOMARATNA, ***A. FREEMAN**;
Univ. of Sydney, Sydney, Australia

**Abstract: Introduction.** Neuronal pathways underlying primate colour vision pass through primary visual cortex. It has previously been shown (Johnson et al., 2001) that neurons in primary visual cortex can be classified according to their responses along an achromatic-

equiluminant axis. Neurons near the achromatic end of this axis respond better to spatial patterns varying in luminance, while cells near the other end of the axis respond more to constant-luminance patterns varying in their long- (L-) and medium- (M-) wavelength content. How does this spread of response type arise? We addressed this question with a signal-processing model focussed on the midget/parvocellular pathway in macaque monkeys. **Methods.** The model comprised neurons ranging in type from cones to excitatory cells in layer 4Cβ of primary visual cortex. Each cell was represented by a differential equation, and all equations were solved simultaneously to obtain response time courses. Cone locations in the visual field were based on a triangular array: L- and M-cones were randomly assigned to array nodes. Ganglion cells were located on a triangular array perturbed with Gaussian deviates in both the horizontal and vertical directions. All geniculocortical synapses were initially assigned the same strength, and a Hebbian development process changed the strengths to optimise cortical responses. The stimulus during development was an achromatic drifting grating, to simulate the effect of retinal waves before eye opening. The grating was presented with a variety of orientations and spatial frequencies. **Results.** After development the model was stimulated with both achromatic and equiluminant gratings. Many cells responded better to achromatic than to equiluminant stimuli, while the reverse was true for other cells, and a substantial number of cells were orientation selective: these findings reflect published work. We also looked at the origins of individual cell preferences. Achromatic-preferring cells owe their preferred orientation to spatial clustering of ganglion cells: off- and on-subfields correspond to higher densities of off- and on-centre ganglion cells, respectively. In contrast, equiluminance-preferring cells have L- and M-dominated subfields that correspond to retinal areas in which most cones are L- and M-type, respectively. **Conclusions.** According to the model, the spread of cell types in primary visual cortex depends on inhomogeneities in the cone and ganglion cell arrays. **Reference.** Johnson EN, Hawken MJ, Shapley R (2001) The spatial transformation of color in the primary visual cortex of the macaque monkey. *Nature Neuroscience*.

**Disclosures: M. Somaratna:** None. **A. Freeman:** None.

**Poster**

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**Program #/Poster #:** PSTR026.03/Y7

**Topic:** D.06. Vision

**Support:** National Science and Technology Innovation 2030 Major Program (2022ZD0204600)

**Title:** Testing Hubel and Wiesel's "ice-cube" model of functional maps in macaque V1 with two-photon calcium imaging

**Authors: *C. YU**, S.-H. ZHANG, S.-M. TANG;
Peking Univ., Beijing, China

**Abstract:** Hubel and Wiesel's famous "ice-cube model" proposed that, V1 orientation and ocular dominance (OD) functional maps intersect orthogonally to optimize wiring efficiency. Although this proposal has gained support from optical imaging studies, maintaining orthogonality among multiple functional maps is geometrically difficult. Moreover, evidence supporting orthogonality mainly comes from pixel-based functional maps, which needs to be validated by cellular information. Here we conducted two-photon calcium imaging of thousands of V1 superficial-layer neurons in FOVs similar in size to hypercolumns (850 x 850 $\mu m^2$) in four awake, fixating macaques. We calculated each neuron's preferences for orientation, OD, and spatial frequency (SF), constructed respective functional maps at cellular resolution, computed the geometric gradients of stimulus preferences with each neuron, and subtracted the intersection angles among gradients. The functional maps demonstrated often complete orientation and OD representations, but limited SF representation (mainly higher SFs) within each FOV. Importantly, intersection angles among orientation, OD, and SF maps were widely distributed without consistent tendencies towards any specific angles. Additional analysis showed similar results when intersections of neurons with high gradients were considered, or when more data points were added to cellular functional maps using a natural neighbor interpolation method before each map was smoothened by a two-dimensional Gaussian ($\sigma$ = 25 $\mu m$). In contrast, Gaussian-smoothened pixel maps showed slight trends of orthogonal (Ori-OD & SF-OD) or parallel (Ori-SF) intersections among maps in some FOVs, resembling previous reports (e.g., Nauhaus et al., 2016). Together our results suggest that V1 hypercolumns, while fully covering at least orientation and ocularity, may have no further geometric constraints to allow coexistence of multiple functional maps. Previous pixel-based results might have been affected by additional factors such as blood vessels and neuropils.

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**Poster**

**PSTR026. Functional Architecture of the Visual System**

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**Topic:** D.06. Vision

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**Title:** Contextual modulation of laminar BOLD profiles in V1

**Authors: *J. EMERSON**[1], K. T. NAVARRO[2], C. A. OLMAN[2,3];
[1]Univ. of Minnesota Grad. Program In Neurosci., Minneapolis, MN; [2]Dept. of Psychology, Univ.

Minnesota, Minneapolis, MN; [3]Ctr. for Magnetic Resonance Res., Univ. of Minnesota, Minneapolis, MN

**Abstract:** In primary visual cortex (V1), both long-range lateral connectivity and feedback from higher order visual areas contribute to shaping neural responses based on spatial context. However, it is unclear exactly how and to what extent lateral and feedback connectivity individually contribute to contextual modulation of neural responses in V1. Developments in ultra-high-field functional magnetic resonance imaging (fMRI) have enabled non-invasive imaging of cortical lamina in humans, which can be exploited to examine the cortical origins of neural signals underlying blood-oxygenation-level-dependent (BOLD) contrast. We acquired data from six participants using 7T fMRI at 0.6 mm isotropic resolution to measure the influence of visual context on BOLD response profiles across cortical depth in V1. Participants viewed sine-wave grating disks (2 cycles per degree, 40% contrast, 2-degree diameter at 3 degrees eccentricity) embedded in 20-degree diameter surround gratings with matched spatial frequency and contrast. Two context conditions were delivered by adjusting either the relative orientation or relative phase of the surround with respect to the target. These were measured against a third condition that lacked any segmentation cues between the target and surround. A fourth surround-only condition was used to assess the effects of feedback on V1 in the absence of feedforward input. The context conditions allowed us to isolate the effects of orientation-tuned surround suppression (OTSS), a canonical example of contextual modulation in V1, from non-orientation dependent figure-ground modulation (FGM). We found significant modulation of BOLD signal in center-selective voxels in the absence of feedforward input, suggesting that feedback and recurrent connections can drive strong BOLD responses in V1. Surprisingly, we found only weak signatures of OTSS that were primarily localized to superficial layers. We conclude that a large fraction of the BOLD signal measured in V1 cannot be attributed to feedforward mechanisms and that feedback appears to modulate the BOLD response broadly across cortical depth.

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**PSTR026. Functional Architecture of the Visual System**

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**Program #/Poster #:** PSTR026.05/Y9

**Topic:** D.06. Vision

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**Title:** Characterizing neurons in anesthetized macaque V1 with multi-photon imaging via a chronically implanted window

**Authors: G. HATANAKA**[1], S. CHATTERJEE[3], K. TAKASAKI[3], T. KIM[1], C. J. M. DYLLA[1], P. BALARAM[3], A. K. PASUPATHY[1], J. WATERS[3], R. C. REID[3], *W. BAIR[2,1];
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**Abstract:** One of our major goals for multi-photon imaging in the macaque primary visual cortex (V1) is to be able to characterize the physiology of as many neurons as possible in a local 3D block of tissue, ultimately allowing functional information to be compared against a connectomic map determined post-mortem. However, to derive meaningful tuning functions from nearly all V1 neurons may require the use of a variety of visual stimuli. Our preliminary results comparing drifting gratings to small flashed spots suggest that neither set alone is sufficient to drive all V1 neurons well and that some regions within the functional architecture contain neurons that are more selective to gratings while other regions contain neurons that are more selective for small spots. We injected a Macaca nemestrina with PHP.eB-CAG-GCaMP6s and PHP.eB-hSyn-GCaMP6s in V1 and implanted a sealed, chronic imaging window with an 8 mm coverglass centered over the injection sites. After 26 days, during which two recovery imaging sessions were carried out to assess wide-field functional architecture (eye dominance and orientation domains), a multi-day, terminal 2-photon imaging session commenced under anesthesia (sufentanil, isoflurane), with paralysis to reduce eye movement. We presented drifting sinewave gratings (size 2-6 deg, 4 Hz, 2 sec duration) to measure direction and spatial frequency preference and presented small, randomly-placed white and black spots (0.2-0.5 deg squares, 7x7 grid, 0.5 sec, gray background) to measure RF location, size and ON/OFF preference. For each ROI (determined by Suite2P), we computed a signal-to-noise ratio (SNR) that divided the modulation in the tuning curve by trial-to-trial variance. We analyzed >10,000 ROIs from 40 fields of view (~440 x 440 um) across >200 um of depth within layer 2/3. We found that ROIs that responded well to sinewaves (top 10% of SNR) tended to occur in clusters that were spatially separated from the ROIs that responded well to small spots, and clusters were broadly consistent across depth in cortex. We observed a much weaker tendency for units to cluster on the basis of receptive field maps that were dominated by ON response vs. those dominated by OFF responses. Our results bear on cortical functional architecture and demonstrate the importance of testing diverse stimulus sets to determine optimal characterization paradigms for activating the vast majority of V1 neurons. We aim to further test this with both multi-photon imaging and high-density electrode recording. In addition to reporting our clustering results, we will describe our novel chronic imaging window and wide-field imaging system.

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**Poster**

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**Title:** Causal optogenetic testing of the role of a retinotopic topographic V1 code in coarse shape perception

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[1]Neurosci., [2]Inst. for Neurosci., [3]Psychology, [4]Ctr. for Perceptual Systems, [5]Ctr. for Theoretical and Computat. Neurosci., Univ. of Texas at Austin, Austin, TX; [6]Neurosurg., Rutgers Univ., New Brunswick, NJ

**Abstract:** Even a simple and localized visual stimulus excites millions of neurons in the primate primary visual cortex, each encoding a small window of visual field, and each with its own selectivity for features such as orientation or spatial frequency. Hence, resolving coarse-scale features—like stimulus shape—requires the pooling of responses across large populations of neurons. The way such information is extracted is an open question. A popular hypothesis has been a *labeled line decoder*—a decoder that knows the specific selectivities of all its individual units and uses that information to identify overall stimulus shape. Our lab has accumulated some support for an alternative hypothesis: a decoder that exploits retinotopy—a topographic organization in the visual cortex in which nearby neurons encode nearby portions of the visual field - creating a one-to-one map of the visual field across the surface of the cortex. Our hypothetical *retinotopic topographic decoder* ignores the selectivities of individual neurons, instead distinguishing shape solely from the retinotopic spread of activity evoked across the cortex. We have trained macaque monkeys in a simple shape discrimination task in which subjects are to report the aspect ratios of small 2-D Gaussian visual stimuli. In parallel, we have developed an all-optical platform for reading out neuronal activity via widefield calcium imaging and simultaneously writing in activity with specific retinotopic shapes using a DMD pattern projector to activate a soma-targeted, red-shifted opsin. Leveraging this setup, we can conduct biasing experiments to attempt to influence animal judgment using artificially induced neuronal activity patterns that only hold information at the retinotopic scale, indiscriminate to tuning properties such as orientation selectivity. We find that injected retinotopic information does affect the perceptual judgment of stimulus shape, systematically biasing the animal's reports of shape as predicted by the retinotopic decoder. To further our interpretation of the results, we performed an *in silico* experiment in a realistic V1 encoding model to see how retinotopic-scale stimulation affects task performances of a labeled line and a retinotopic decoder. *In silico*, we observed no systematic biasing effects for a labeled line decoder in response to retinotopic-scale stimulation, contrasting the bias seen in our experimental results. Therefore, our preliminary

results provide the first direct evidence for a retinotopic topographic decoder, indicating that the coarse retinotopic spread of activity across the surface of the cortex is an integral part of the neural code for stimulus shape.

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**Title:** Neural mechanisms mediating population size tuning and surround modulation in macaque V1

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**Abstract:** The responses of many neurons in primate V1 decrease when a stimulus exceeds an optimal size, and this effect varies with the properties of the surround stimulus. The mechanisms mediating such size tuning and surround modulation effects are not known. The goal of the current study is to examine specific hypotheses regarding those underlying mechanisms at the population level, focusing on the role of V1 inhibition and the interplay between feedforward inputs, recurrent computations within V1, and feedback from higher visual areas. To address this goal, we took advantage of the cell-type specificity afforded by viral approaches and used widefield imaging of the genetically encoded calcium indicator GCaMP6f in macaque V1 to record responses from either excitatory populations, via the CaMKIIa promoter, or inhibitory populations, via the pan-inhibitory h56D promoter (Mehta et al., 2019). We compared V1 responses across the two cell classes to predictions of three candidate models of size tuning: suppressive surround, supralinear stabilized network (SSN), and a model where size tuning in V1 is inherited from LGN inputs. Our results do not support any of these models, demonstrating 1) similar size tuning responses to flashed circular sine wave gratings of increasing size across cell types and stronger surround modulation in inhibitory vs. excitatory cells, inconsistent with suppressive surround, 2) similar contrast response functions to large flashed sine wave gratings

across cell types, inconsistent with SSN, and 3) selective surround effects to stimuli with center and surround discontinuities of either orientation or phase, inconsistent with surround modulation solely inherited from LGN inputs. Instead, we find highly elevated V1 population activity along the retinotopic representation of the occluding edge that is formed when a center and surround differ in orientation or only in phase. Given these results, we propose an alternative model wherein size tuning and surround modulation are mediated by a recurrent or feedback mechanism that facilitates V1 population response within a short distance from the representation of occluding edges. This elevated occluding-edge response is withdrawn from the center population as stimulus size increases, leading to the observed population size tuning and surround modulation. We are currently developing a population model that captures these results. Future work will test the predictions of this occluding-edge model of surround modulations.

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**Title:** Columnar-scale optogenetic stimulation of macaque V1 biases perceptual judgment of orientation

**Authors: *P. K. TAN**[1], S. KOBAYASHI[1], G. BENVENUTI[1], S. C.-Y. CHEN[2], Y. CHEN[1], E. SEIDEMANN[1];
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**Abstract:** The primate primary visual cortex (V1) is functionally organized into two-dimensional topographic maps that represent visual features. One such feature is orientation, which is encoded at both a fine-scale of single neurons and a coarse-scale of orientation columns containing thousands of neurons. A key open question is whether downstream circuits exploit this coarse columnar-scale topography as part of the neural code for orientation - i.e., a topographic code hypothesis. The alternative is that decoding circuits take into account the specific tuning properties of each neuron in the population (labeled-line hypothesis). To causally test the topographic code hypothesis, we first developed optical-genetic methods for

simultaneous read-write in the cortex of a behaving macaque. We used viral vectors to co-express GCaMP6f and soma-localized ChRmine in V1 excitatory neurons (expression area of ~16mm2). We then identified orientation-selective columns via widefield calcium imaging, prior to the simultaneous recording and stimulation (i.e. 'read-and-write') of sets of columns with widefield imaging (sCMOS camera) and patterned optogenetics (DMD-projector). Second, we asked whether optogenetic stimulation (optostim) that mimics the columnar response to an oriented visual stimulus can bias perceptual judgments of orientation towards the orientation preferred by the stimulated columns. We trained a macaque monkey to perform a coarse orientation discrimination task on horizontal or vertical gabors presented at 4-5 contrast levels to vary difficulty. Within each block, in each trial we randomly stimulated either vertical, horizontal or no columns as the visual Gabor was presented. The animal was rewarded only for correct judgments on visual stimuli. We found, for the first time, that columnar optostim of vertical or horizontal columns significantly biases the animal's orientation judgments in the expected direction, and such biasing is reflected in simultaneously measured optostim-driven columnar-scale neural responses in V1. Our preliminary results provide strong causal evidence in support of the topographic code hypothesis, particularly as the animal is only rewarded for correct judgments of the visual gabor and is thus incentivized to ignore the optogenetic stimulation. Further, our work provides a foundation for the next-generation of cortical neuroprosthetics, where feature-specific signals can be inserted in large contiguous cortical areas via columnar-scale stimulation.

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**Title:** Different roles of response covariability and its attentional modulation in sensory cortex and posterior parietal cortex

**Authors: *Y. JIANG**[1], *Y. JIANG[3], *Y. JIANG[4], S. HE[2], J. ZHANG[5];
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**Abstract:** The covariability of neural responses in the neuron population is highly relevant to the information encoding. Cognitive processes, such as attention, are found to modulate the covariability in visual cortex to improve information encoding, suggesting the existence of computational advantage of covariability modulation in the neural system. However, is the covariability modulation a general mechanism for enhanced information encoding throughout the information processing pathway, or is it only adopted in certain processing stages, depending on the property of neural representation? In this study, we used ultra-high-field MRI and a slow event-related design to investigate the covariability in neural responses of V1 and posterior parietal cortex (PPC) in the human brain under different attention states. In each trial, after a spatial cue, two gratings were briefly presented in different visual fields. Participants (n=11; five females; aged 23 to 28 years) had to discriminate the orientation of the cued grating. Covariability was estimated by calculating the noise correlation of trial-to-trial fMRI response variabilities between each voxel pair, and the quality of information encoding was estimated by the decoding performance of orientation information in each brain region. Our results showed that while attention decreased the covariability to improve the stimulus encoding in the early visual cortex, covariability modulation was not observed in PPC, where covariability had little impact on information encoding. Further, attention generally promoted the information flow between early visual cortex and PPC, which was partially contributed by a flow from high- to low-dimensional representations, suggesting the existence of a reduction in the dimensionality of neural representation from early visual cortex to PPC. Finally, the neural response patterns in PPC could predict the amplitudes of covariability change in early visual cortex, indicating a top-down control from PPC to early visual cortex. Our findings reveal the specific roles of sensory cortex and PPC during attentional modulation of covariability, determined by the complexity and fidelity of the neural representation in each cortical region.

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**Title:** Differential effects of continuous theta burst stimulation on motor thresholds and visual phosphenes

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**Abstract:** Theta burst stimulation (TBS) is a repetitive transcranial magnetic stimulation (rTMS) protocol with the added benefit that it requires shorter stimulation time compared to traditional rTMS protocols. This increases efficiency and compliance in both research and clinical settings. Even though TBS applications in the primary motor cortex (M1) have been well-explored, scant attention has been paid to its impact on the primary visual cortex (V1) and parameter optimisation. TBS includes two variants: Intermittent TBS (iTBS; excitatory) and continuous TBS (cTBS; inhibitory). In our lab, previous neuroimaging studies including magnetic resonance spectroscopy (MRS) and resting state functional magnetic resonance imaging (rs-fMRI) did not lead to notable alterations in gamma-aminobutyric acid (GABA) concentration in V1 or functional connectivity in whole-brain analyses when V1 was stimulated with either cTBS or iTBS (Cohan et al., 2023; Stoby et al., 2022). However, we previously found significant effects when applying low frequency (1Hz) rTMS to V1. This emphasises the need to understand TBS effects on visual brain areas and optimise TBS protocols accordingly (Rafique et al., 2016; Rafique & Steeves, 2020, 2022). In this study, we explored cTBS' influence on M1 and V1 utilising MRI-guided stereotactic neuronavigation. We investigated the disparities in biophysical parameters such as scalp-to-cortex distance (SCD), electric fields at hotspots and stimulation intensities between M1 and V1. We used motor thresholds (MTs) for M1 stimulation and phosphene thresholds (PTs) for V1 stimulation as markers. Our preliminary results suggest that PTs are significantly higher than MTs despite longer SCD at V1, and shorter SCD at M1. In addition, we found that post-cTBS PTs increased in comparison to sham stimulation, hinting at an inhibitory aftereffect. However, both active and sham cTBS in M1 yielded to increased MTs. A profound understanding of the varied stimulation parameter effects and their location-specific variations is crucial for effective and efficient TMS protocol application in research and therapeutic contexts. These insights will facilitate tailoring TMS approaches to each target region's unique requirements, enhancing the overall effectiveness of TBS in vision research and clinical settings.

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**Title:** The hierarchical convolutional energy model: a biologically plausible model that explains spatial, chromatic, and temporal tuning in V4 neurons

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**Abstract:** Area V4 is an intermediate processing stage of the ventral visual stream. V4 neurons are selective for color and for shape features of intermediate complexity (e.g., curved edge elements and non-Cartesian gratings). However, current computational models of V4 neurons cannot predict more than a fraction of the response variance observed under naturalistic conditions. Thus, we performed long-term, large-scale neurophysiological recordings of V4 neurons during stimulation with full-color nature videos. This produced a data set of unprecedented size, consisting of up to 7 hours of 60Hz video data recorded from single V4 neurons. We then developed the biologically plausible hierarchical convolutional energy model (HCE). In this model, a stimulus is first log-polar-transformed to mimic cortical magnification in V1. Then, it is passed through a stack of simple and complex cell subunits, which represent the visual hierarchy from V1 to V4. The HCE model was fit separately to each of the 326 V4 neurons in the sample. The fit models achieved high prediction performance on a withheld test set. Each model was used to synthesize a predicted optimal pattern (POP) video, which is predicted to elicit the maximal response of the corresponding neuron. These POPs were analyzed to recover the spatial, chromatic and temporal tuning properties of the V4 population. The POPs recapitulate previous findings from V4 and reveal new V4 tuning properties. For example, in the spatial domain V4 neurons differ in their tuning for low versus high frequencies, radial versus concentric gratings, texture versus contour, and contour curvature. In the color domain V4 neurons differ in their selectivity for monochromatic versus color patterns, and for blue-yellow, green-magenta and red-cyan patterns. Finally, in the time domain V4 neurons vary from fast phasic (peak 33-50 ms from stimulus onset), slow phasic (peak 67-83 ms from stimulus onset), and sustained patterns. In a control, we found that the HCE model outperforms a cartesian HCE model. POPs from the cartesian model are less likely to contain curves, possibly because the model builds curves using multiple aligned edges. In contrast, the log polar transform allows the HCE model to produce curves as a function of edge orientation. Currently, the HCE model is the only biologically plausible spatiotemporal model to accurately predict V4 responses under naturalistic conditions. POPs produced from this model consist of multiple overlapping spatial frequency, orientation, and color patterns. These patterns suggest that V4 neurons represent amplitude-modulated filters, which may play a critical role in scene segmentation of the natural world.

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**Title:** Sustained and transient responses in human visual cortex

**Authors: *Q. WANG**[1], L. LUO[2], F. FANG[1];
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**Abstract: TITLE: Sustained and transient responses in human visual cortex**
**ABSTRACT:**The temporal dynamic features of perceptual neurons encode rich information that allows us to adapt to the rapidly changing world. Previous neuroimaging and computational model studies have proposed a two-channel model in the visual system. According to this model, temporal processing in visual cortices is mediated by a sustained channel showing lasting responses throughout stimulus presentations and a transient channel showing rapid responses to stimulus onsets and offsets. However, direct empirical evidence supporting this model has been lacking. To address this gap, we utilized intracranial electroencephalogram (iEEG) to investigate and characterize these channels within the human visual cortical hierarchy.We recorded iEEG data from 26 participants (7 females) with drug-resistant epilepsy who underwent stereo-electrode implantation for clinical purposes. Using 3° x 3° checkerboard stimuli presented at different spatial positions (Experiment 1), we identified 211 sites with robust visually evoked high gamma activities (HGAs) across the primary visual cortex (V1, n = 67), lower visual cortex (V2-V3 or LVC, n = 80), and higher visual cortex (HVC, n = 64). We found that sites across the visual hierarchy exhibited sustained or transient-like HGA profiles in response to visual stimuli at their receptive field (RF) centers, with a stronger weighting towards the transient channel as the RF eccentricity increased. Interestingly, when the stimulus was moved from the RF center to the RF edge, we observed more transient responses in the sustained sites, indicating that the sustained channel possesses superior spatial resolution. Additionally, we found that the sustained sites in V1 received stronger feedback modulations compared to transient sites when stimulated at the RF center, with this difference diminishing when stimulated at the RF edge. We further presented a subset of participants (n = 8) with grating stimuli (Experiment 2). Our findings revealed that sustained sites demonstrated more temporally stable encoding of orientation features
than transient sites. In summary, our study provides a comprehensive characterization of the sustained and transient channels in the human visual system. We highlight their distinct characteristics, including the topological distribution, receptive field structure, connectivity patterns, and feature encoding properties. These findings offer fundamental support for a unified theoretical framework elucidating the dynamic encoding mechanism of visual information.

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**Title:** Waves traveling over a map of visual space can ignite short-term predictions of sensory input

**Authors:** G. BENIGNO[1], R. C. BUDZINSKI[1], Z. DAVIS[2], J. H. REYNOLDS[2], ***L. MULLER**[1];
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**Abstract:** Recent analyses have found waves of neural activity traveling across entire visual cortical areas in awake animals. These traveling waves modulate the excitability of local networks and perceptual sensitivity. The general computational role of these spatiotemporal patterns in the visual system, however, remains unclear. Here, we hypothesize that traveling waves endow the visual system with the capacity to predict complex and naturalistic inputs. We present a network model whose connections can be rapidly and efficiently trained to predict individual natural movies. After training, a few input frames from a movie trigger complex wave patterns that drive accurate predictions many frames into the future solely from the network's connections. When the recurrent connections that drive waves are randomly shuffled, both traveling waves and the ability to predict are eliminated. These results suggest traveling waves may play an essential computational role in the visual system by embedding continuous spatiotemporal structures over spatial maps.

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**Title:** Shared connectome and organization in the human high-level visual cortex irrespective of sensory experience

**Authors: *G. JIAHUI**[1], F. SETTI[2], M. FEILONG[1], D. BOTTARI[2], M. GOBBINI[3], P. PIETRINI[2], E. RICCIARDI[2], J. V. HAXBY[1];
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**Abstract:** Human high-level visual cortex selectively responds to different categories (e.g., faces, places). To what extent is sensory experience a mandatory prerequisite for this functional architecture to arise and develop? In this study, congenitally blind and deaf participants were presented with audio-only and video-only versions of the live-action movie 101 Dalmatians, respectively. Three control groups of participants either watched and/or listened to the audiovisual, the audio-only, and the video-only versions of the movie. Using fMRI data from an independent group of participants who watched the feature movie, The Grand Budapest Hotel, and performed a visual category functional localizer task, individualized category-selective topographies were successfully predicted in either congenitally blind or deaf participants by projecting the localizer data into their individual cortices using transformation matrices based on connectivity hyperalignment. Specifically, category-selective topographies in the ventral visual pathway in congenitally blind participants were highly comparable to those in sighted participants. Functional connectomes were notably similar across the entire cortex, regardless of the modality of sensory input or the content of the stimuli. When visual or auditory information was shared between groups, participants' connectomes showed higher similarity in the corresponding visual and auditory cortices. Connectomes in the bilateral superior temporal cortices, which are involved in multisensory information processing, were analogous across all participant groups. Thus, this study, under real-world conditions, demonstrates that the connectome maintains a similar organization across varying sensory modalities and content, and shows that development of the functional organization of the human high-level cortex can occur independently of prior sensory experience.

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**Title:** Multimodal integration of fMRI, dMRI and cytoarchitectonics in macaque visual cortex.

**Authors: *P. BALARAM**[1], A. HELLEVIK[1], B. MACLENNAN[1], E. E. TURSCHAK[1], J. TANDUKAR[2], K. TAKASAKI[1], R. TORRES[1], C. LAUGHLAND[1], O. GLIKO[1], D. VUMBACO[1], R. GAO[2], D. Y. TSAO[3], R. C. REID[1];
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**Abstract:** Visual cortical areas contain complex neural ensembles that segregate information into discrete processing streams to efficiently represent features like form and motion in complex visual scenes. Studies of these neural ensembles have benefitted from technical advances in functional imaging and neuroanatomy, and methods for coregistration of functional and anatomical datasets across multiple brain areas are now crucial to advancing our knowledge of visual cortical circuitry. We collected fMRI, dMRI and cytoarchitectonic data spanning cortical visual areas V1 through V4 in adult macaque monkeys, to examine correlations between functional and anatomical measures of areal and modular boundaries across macaque visual cortex. fMRI was collected using a 3T Siemens scanner, using localizers for retinotopy, color, motion, and category-selective domains (eg. face patches) to document functional and modular boundaries across visual areas. Postmortem 3T dMRI was collected following transcardial perfusion with paraformaldehyde, to document the anatomical location and orientation of major fiber tracts underlying visual cortex and evaluate macroscale shifts in brain size between pre- and post-mortem scans. Perfused brain tissue spanning V1 through V4 was cryosectioned coronally at 100μm and fluorescently labeled to identify cell nuclei (DAPI), myelin basic protein (MBP), non-phosphorylated heavy-chain neurofilaments (SMI32) and parvalbumin (PV). These four histological stains, when combined in individual sections, consistently identify cortical areal boundaries, laminar and modular boundaries within cortical areas, excitatory (SMI32-positive) and inhibitory (PV-positive) cell types, and individual axonal trajectories within white matter tracts. Coregistration of all data modalities is ongoing, and preliminary work demonstrates correlations between areal and modular boundaries of early visual cortical areas across functional and anatomical datasets. Future work will integrate optical physiology and spatial transcriptomics with the current experimental modalities, which will provide single-cell measures of transcriptomic cell type and neural function within the areal and modular boundaries identified by fMRI, dMRI and cytoarchitectonics across macaque visual cortex.

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**Poster**

**PSTR026. Functional Architecture of the Visual System**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR026.16/Z1

**Topic:** D.06. Vision

**Support:** R01 EY032125
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DMS-1412722

**Title:** A Novel Quantitative Analysis of Human Visual Processing Cascade

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**Abstract:** Humans perceive the world veridically and this is largely invariant across individuals. What we "see" is a complex process that involves a cascade of transformations of the retinal image in visual cortical areas. We know from retinotopic mapping studies that visual inputs are distorted when they are projected onto the cortical surface of the brain. So do these distorted projections have any relations to one another and how do they ultimately transform our distorted projections of the physical world into a non-distorted percept? High resolution fMRI scans of retinotopic visual areas (V1, V2, V3) have shown us that retinal images are distorted at each step of the visual processing cascade. Precisely how much visual inputs are distorted when moving through the visual processing cascade has largely remained unexplored. We quantified the geometric distortions of the retinal image projections on visual areas V1 and V2 for each quadrant of the visual field (upper left, upper right, lower left, lower right) using the recently proposed quasiconformal quantification framework (Ta, et al., 2021), which is based on the principles of computational conformal geometry and quasiconformal Teichmuller theory. It can precisely quantify the amount of distortions in retinal image projections onto cortical surfaces with the Beltrami coefficient (BC), a differential geometry concept that measures angle distortions in quasiconformal maps. We compared distortions of the retinal image in visual areas V1 and V2 using their computed Beltrami coefficient maps (BCM) from Human Connectome Project(n=181) retinotopic data. The average BC magnitude from the visual field to visual areas V1 and V2 by region (left dorsal, left ventral, right dorsal, right ventral) was V1=(0.497±0.187, 0.500±0.184, 0.337±0.135, 0.339±0.133) and V2=(0.484±0.206, 0.573±0.191, 0.307±0.140, 0.446±0.135). The results suggest that retinal image projections between V1 and V2 have similar distortions in the dorsal region (lower quadrants of the visual field) [ZLL1] but significantly higher distortions in the ventral region (upper quadrants). With better fMRI data for higher level visual cortical areas, we plan to investigate if this result also holds true.

**Disclosures:** **D. Ta:** None. **Z. Lu:** A. Employment/Salary (full or part-time); New York University. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); New York University. **Y. Wang:** A. Employment/Salary (full or part-time); Arizona State University. E. Ownership Interest (stock,

stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Arizona State University.

**Poster**

**PSTR026. Functional Architecture of the Visual System**

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**Topic:** D.06. Vision

**Support:** US National Science Foundation grant 2219323
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**Title:** Brain network processes underlying the generation of hundreds of visual category responses in the human brain

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**Abstract:** How does the human brain make sense of complex naturalistic visual stimuli? While many models have been developed to tackle this problem, activity flow (ActFlow) models can provide unique insights into the network processes underlying visual comprehension. ActFlow modeling is a flexible analysis approach that uses empirical brain connectivity to simulate the generation of task-evoked brain activations. This provides empirically supported insights into how neurocognitive processes, including face selectivity in the fusiform face area (FFA), are generated from the flow of activity across brain connections. However, their application to the dynamic and complex stimuli of movie data, known for their ability to rapidly probe a variety of neurocognitive functions, remains uncharted territory. We hypothesized that ActFlow models, when applied to movie data, would not only replicate established category selectivity but also accurately predict the brain's response to a wide range of stimuli. The analysis was conducted on the high resolution 7T movie watching Human Connectome Project (young adult) fMRI dataset. This dataset includes 859 diverse features from visual and auditory stimuli to complex actions. As a proof of concept, we focused our analysis on face selectivity in FFA. Face selectivity was calculated as the ratio of activation for faces in FFA to the average activation for all other features in that area. Next, we simulated the network processes driving activation in FFA using an Actflow model, which considers both the resting-state functional connectivity of that region with all others and their actual activations. Moreover, to account for stimulus-driven simulation of FFA activity, we employed the ActFlow model based on the primary visual cortex (V1) activation and functional connections and observed significant face selectivity in FFA. Lastly, we extended the ActfFlow model to generate activations for all 859 movie features and all 360 cortical brain regions, indicating robust predictions of response profiles (population receptive

fields; p-values<0.0001, Bonferroni corrected). Importantly, this demonstrates that our methodology can be extended to investigate category selectivity in a wide variety of brain regions. There is also potential to construct empirical encoding models for brain areas like V1, to better understand the transformations leading to complex representations such as category selectivity. Overall, these results demonstrate that network encoding models explain various visual and non-visual neural responses, setting the stage for broader investigations into the generation of brain-wide information dynamics.

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**Poster**

**PSTR027. Plasticity of the Visual System in Health and Disease**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR027.01/Z3

**Topic:** D.06. Vision

**Support:** NIH Grant U01EY025858

**Title:** Macular Degeneration and Plasticity: a newly shared dataset available as part of the NIH Connectomes in Human Diseases project

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**Abstract:** We present a shared functional and structural MRI dataset that can be used to advance our understanding of plasticity in the human visual system. Macular degeneration refers to a group of diseases of the retina that result in their late stages in loss of photoreceptors in the macula, the part of the retina responsible for central vision. After central vision loss, patients' visual experiences are profoundly altered. Central vision can no longer serve its typical functions: e.g., reading, examining attended objects, etc. To the degree that patients use vision in daily life, they must learn to use peripheral vision. This represents a massive change in attentive use of the brain circuits that support peripheral vision.The Macular Degeneration and Plasticity project is part of the Human Connectome Project, Connectomes in Human Diseases. We collected data from patients with macular degeneration, and age, gender, and education-matched controls, allowing group-level comparisons examining the effect of MD. Use of participants with MD also supports a within-subject approach to examining brain plasticity. Participants with macular degeneration have portions of the visual field which lose sensation (scotoma), portions where input stays the same (spared peripheral visual fields), and many participants have a

portion of the visual field that is regularly used for attention-demanding tasks (preferred retinal locus). Because many brain areas are retinotopically mapped, these different portions of the visual field are represented in distinct regions of the cortex. Thus, this dataset allows examination of the impact of both increased and decreased usage in the same participant. These data will be available for examining plasticity in a macular degeneration model. We include partial datasets in the repository to increase the utility of the dataset for a range of uses; there are 38 participants with macular degeneration and 30 controls. Briefly, datasets, collected over 6 extensive sessions include: MRI measures, retinal health, behavior, neuropsychology, and demographics. This dataset has produced a number of interim publications, and will be available to the public on the NIMH Data Archive and the Connectome Coordination Facility. We look forward to the innovative analyses that the neuroimaging community will perform on this singular dataset, which has potential to help the field understand the scope of neural plasticity in the visual system.

**Disclosures: K.M. Visscher:** None. **P.D. Stewart:** None. **P. Demirayak:** None. **L.L. Fleming:** None. **M.K. Defenderfer:** None. **M. Maniglia:** None. **S. Nolin:** None. **M. Biles:** None. **D. DeCarlo:** None.

**Poster**

**PSTR027. Plasticity of the Visual System in Health and Disease**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

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**Topic:** D.06. Vision

**Support:** EU Horizon 2020 No. 641805
DFG HO 2002/12-1

**Title:** Stability and plasticity of vision in the absence of functioning cones - scotopic and photopic conventional visual acuity and hyperacuity in achromatopsia

**Authors: *M. B. HOFFMANN**[1], M. BACH[2], B. KAESMANN-KELLNER[3], I. WIELAND[4], F. H. STOLLE[1], A. HERBIK[1];
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**Abstract:** Achromatopsia (ACHM) is a rare inherited disorder rendering retinal cone photoreceptors non-functional. As a consequence, the sizable foveal representation in the visual cortex is congenitally deprived of visual input. This spurs the hypothesis that the cortical representation of the central visual field in achromatopsia patients is remapped to take up processing of paracentral inputs (Baseler et al. 2002). Such plasticity might result in an enhancement of visual functions that are limited by cortical resources, such as visual hyper-

acuity. At the same time, they might confound the success of current target developments of gene-addition therapies in ACHM (Michalakis et al. 2022). To test the hypothesis that visual hyperacuity is increased in ACHM in particular for scotopic conditions, we compared conventional visual acuity (cVA) and hyperacuity (hVA) in ACHM (n=8; 6 CNGB3-related and 2 CNGA3-related; age range: 16 - 53 years; ERG-confirmed absence of cone function) and age-matched controls (HC, n=7). We applied photopic (maximal luminance 220 cd/m2) and scotopic conditions (maximal luminance 0.004 cd/m2; 40 min of dark adaptation) for white optotypes on black background to reduce glare effects in ACHM (Freundlieb et al. 2020). For photopic conditions both cVA and hVA were significantly worse in ACHM compared to HC, i.e., resulting in higher logMAR VA-values in ACHM (HC vs ACHM: cVA 0.0±0.04 vs 1.0±0.11; hVA -0.9±0.09 vs 0.5±0.22). For scotopic conditions there was a non-significant trend to worse cVA and hVA in ACHM (HC vs ACHM: cVA 1.0±0.04 vs 1.23±0.05; hVA -0.1±03 vs 0.1±0.08). In sum, for the critical scotopic testing condition, if any effect, there is a reduction of visual acuity (cVA and hVA) in ACHM. In conclusion, no improvement of visual function is found in ACHM that might indicate functionally relevant visual cortex plasticity. This is in line with recent MRI investigations that indicate the lack of maturation of various aspects of visual cortex structure and function in ACHM (Lowndes et al. 2021; Molz et al. 2022).

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**Poster**

**PSTR027. Plasticity of the Visual System in Health and Disease**

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**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR027.03/Z4

**Topic:** D.06. Vision

**Support:** R01 EY027193
Holland Trice Award

**Title:** Computational manifold identifies gene products responsive to genetic correction of retinal degeneration

**Authors:** M. THAPA[1], L. DYBALLA[3], E. L. HORNING[4], A. P. SAMPATH[1], J. CHEN[5], S. ZUCKER[3], G. D. FIELD[1], ***M. L. SCALABRINO**[2];
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**Abstract:** The death of photoreceptors in inherited retinal disorders, e.g. retinitis pigmentosa, can lead to blindness. Since photoreceptor death induces remodeling of bipolar cells (BCs), it is likely mediated by altered gene expression. We utilized a gene-embedding manifold to ask how BC transcriptomes change as a consequence of degeneration and genetic correction in a mouse model of retinitis pigmentosa. Mice with a floxed neomycin cassette inserted into the Cngb1

locus (*Cngb1*$^{neo/neo}$) were crossed with *Grm6-GFP* mice; offspring exhibit slow rod degeneration and express green fluorescent protein (GFP) in ON BCs. Littermates heterozygous for the neomycin cassette were controls. In the uncorrected degeneration group, retinas were sampled at P30 (70% rod loss and 2% cone loss), P90 (30% rod loss and 5% cone loss), and P210 (96% rod loss and 35% cone loss). Therapy was performed early (P30) and late (P90); retinas harvested at P150. Mice were sacrificed, retinas dissociated using papain, and sorted via FACS into GFP+ and GFP- cell populations at these times. RNA was extracted from (relatively) pure populations of sorted BCs and bulk RNA sequenced using Illumina MiSeq. Data were analyzed using manifold learning: genes with similar expression levels were near each other, and neighborhoods of genes identified those that follow similar expression trajectories. We found >2000 genes differentially expressed in ON BCs throughout photoreceptor degeneration in the *Cngb1*$^{neo/neo}$ ON BC transcriptome. Gene families known to change during degeneration, such as synaptic signaling, neuron projection, and stress response, had results predicted from prior studies, confirming the methodology. Importantly, developmental genes were largely upregulated over time in *Cngb1*$^{neo/neo}$ ON BCs but downregulated in heterozygous cells, independent of age-related genes. However, genes related to synaptogenesis were not upregulated as a class, suggesting rewiring bipolar cells failed to create new synapses. Finally, we found degeneration-affected gene subsets that were uncorrected by gene therapy, some that were corrected by therapy, and a distinct subset differing from both controls and degenerated. These results provide new avenues for therapeutic targets related to preventing or reversing remodeling, as well as inducing neuroplasticity for cell replacement and regenerative technologies for photoreceptor degenerations.

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**Poster**

**PSTR027. Plasticity of the Visual System in Health and Disease**

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**Program #/Poster #:** PSTR027.04/Z5

**Topic:** D.06. Vision

**Support:** R21 EY031520

**Title:** Impact of retinal excitotoxic lesions on responses of dorsal lateral geniculate nucleus neurons in the ferret.

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**Abstract:** The dorsal lateral geniculate nucleus (LGN) of the thalamus is driven by inputs from retina, which are then relayed to primary visual cortex. Diseases like glaucoma that impact

retinal ganglion cells (RGCs), the output neurons of the retina, can cause loss of driving inputs to LGN neurons. However, surprisingly little is known about neurophysiological changes in the LGN following RGC damage. Prior work showed that LGN neurons with receptive fields immediately surrounding the lesion-projection zone (LPZ) of a laser-induced retinal scotoma shifted their receptive fields (Eysel et al.,1982, Nature). Here, we asked if RGC damage leads to other changes in LGN responses, and if the X and Y parallel processing streams are similarly or differentially impacted. We hypothesize that RGC damage would differentially impact X and Y neuronal responses to visual stimuli, since transmissions of visually-evoked activities from RGCs to LGN neurons in cats are selectively modulated in X channel but not in Y channel(Bullier and Norton, 1979, Journal of Neurophysiology), and these differences would depend on distance to the scotoma. To kill RGCs, we injected 5 µL of 2mM kainic acid (KA), an excitotoxin, intravitreally into a single eye in ferrets. Before and after the injection, we measured the thickness of the RGC layer complex (RNFL+IPL+GCL) using Optical Coherence Tomography (OCT). We then used multi-electrode arrays to record the responses of LGN neurons to a variety of visual stimuli both contralateral and ipsilateral to the retinal lesion in anesthetized and paralyzed ferrets. We estimated the relative eccentricities of recorded LGN neurons based on electrode tracts, in addition to computing the area and eccentricity of RGC loss histologically. We found that a significant portion of LGN neurons with receptive fields in the LPZ were unresponsive or lacked tuning to visual stimuli. LGN neurons with receptive fields near the scotoma boundary often lacked tuning for spatial frequency and showed altered tuning to luminance contrast and temporal frequency. These tuning shifts were present in both sustained (X) and transient (Y) LGN neurons. Sustained/X neurons displayed greater variability in baseline firing rates and response latency relative to transient/Y neurons. These data suggest significant shifts in tuning responses among LGN neurons with receptive fields in or near the LPZ, regardless of cell type. However, sustained/X neurons appeared more impacted in terms of response timing and precision. Our findings lay the groundwork for ongoing efforts to recruit and restore visual processing at multiple levels of the visual system after retinal lesions.

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**Poster**

**PSTR027. Plasticity of the Visual System in Health and Disease**

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**Program #/Poster #:** PSTR027.05/Z6

**Topic:** D.06. Vision

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**Title:** Opposing effects of short-term monocular contrast deprivation in the human lateral geniculate nucleus and high-order visual cortex

**Authors: *Y. QIAN**[1], Z. SUN[2], C. QIAN[3], Y. GAO[4], J. ZHOU[5], P. ZHANG[6];
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**Abstract:** Although experience-dependent ocular dominance (OD) plasticity has been extensively studied in the primary visual cortex (V1), little is known about the subcortical nuclei and high-order visual cortex. Using high-resolution 7T fMRI, we found two distinct but cooperating adaptive mechanisms in the visual thalamus and high-order visual cortex of human adults. Short-term monocular deprivation (MD) of contrast input significantly enhanced the deprived eye's sensitivity compared to the nondeprived eye in the parvocellular subdivisions of the lateral geniculate nucleus (LGN) and the ventrolateral pulvinar, but not in the superior colliculus. Although the deprivation effect in V1 varied substantially across subjects, it showed significant correlation with and feedback connectivity to the LGN in the binocular but not monocular stimulus conditions. Perceptually, the deprived eye became more sensitive in contrast detection and more dominant in binocular phase combination. In the lateral occipital area (LO) and V3ab, MD enhanced the nondeprived eye's sensitivity and their connectivity from V1. Inputs to the nondeprived eye also generated faster and more accurate 3-D shape-from-shading perception. These opposing MD effects demonstrate that in the adult human brain, homeostatic mechanism in the visual thalamus cooperates with Hebbian-like mechanism in the high-order visual cortex to rapidly and adaptively adjust interocular balance to abnormal binocular inputs. Using high-resolution 7T fMRI, we show that short-term MD in human adults shifts interocular balance to the deprived eye in the LGN of the thalamus, but to the nondeprived eye in high-order visual cortex. Eye dominance in low-level and high-level visual perception also changes in opposite directions. These findings demonstrate that homeostatic adaptive mechanism in the visual thalamus cooperates with Hebbian-like mechanism in the high-order visual cortex to rapidly and adaptively adjust interocular balance to abnormal binocular inputs.

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**Poster**

**PSTR027. Plasticity of the Visual System in Health and Disease**

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**Program #/Poster #:** PSTR027.06/Z7

**Topic:** D.06. Vision

**Support:** NIH EY030434

**Title:** Short-term monocular deprivation impacts the ocular dominance columns of adult visual cortex

**Authors: *D. Y. TS'O**[1], R. A. MILLER, III[2], M. BEGUM[1], I. AGANJ[3,4], S. NASR[3,4]; [1]Neurosurg., [2]Neurol., Upstate Med. Univ., Syracuse, NY; [3]Athinoula A Martinos Ctr. for Biomed. Imaging, MGH, Charlestown, MA; [4]Radiology, Harvard Med. Sch., Boston, MA

**Abstract:** Normal interocular balance, the relative strengths of left and right eye inputs to the central visual pathways, is an important prerequisite for normal binocular vision. Human psychophysical studies have demonstrated a disruption of interocular balance following a period of short-term (1-3 hours) monocular deprivation (STMD). The unexpected outcome of STMD is a relative increase, not decrease, in the deprived eye (DE) gain post-STMD. This example of adult neural plasticity is opposite in sign to that expected by traditional monocular eye-patching. The mechanisms underlying this STMD response are largely unknown. We have previously conducted functional optical imaging STMD studies in V1 of adult macaque monkeys, demonstrating an increased V1 response to DE stimuli relative to non-deprived eye (NDE) stimuli after STMD. Multiple single-unit recordings additionally revealed correlates of the STMD paradigm in V1, most notably the alteration of responses during and after STMD of neurons that are dominated by the NDE even though the stimuli provided to the NDE is unaltered during the STMD. These alterations of the NDE-dominated neurons include a greater shift in the post-STMD responses to the DE and a disruption of the pattern of the NDE ocular dominance columns (ODCs). We further explored these STMD sequelae in human V1 through high-resolution 7T fMRI, enabling the measurement of activity specific to each of the two sets of ODCs, before, during and after STMD. A preliminary study was conducted in a male subject with normal vision. Baseline (before) scans were conducted prior to STMD, afforded by a translucent patch over the right (dominant) eye. The STMD lasted 8 hours, with "during" scans conducted at 2, 4 and 8 hours, followed by an "after" STMD (unpatched) scan. As with the primate studies, the DE responses post-STMD were elevated relative to baseline, primarily in the NDE ODCs. Overall, the NDE-stimulated responses were elevated during STMD, dropping back to baseline levels post-STMD. The same fMRI sessions included resting state (eyes closed) functional connectivity (FC) measurements. STMD also influenced the level of FC between ODCs. Before STMD, there was a stronger FC between ODCs with alike compared to unalike ocular preference -- STMD increased this bias. However, for pairs of ODCs with shorter distances (<16 mm), this effect was short-lived, reversing post-STMD, whereas for pairs with longer distances (>21 mm), the increased like-like ODC FC was still evident even after patch removal. These human fMRI results largely matched the prior primate studies and extend our understanding of the impact of STMD on the binocular interactions in early visual cortex.

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**Poster**

**PSTR027. Plasticity of the Visual System in Health and Disease**

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**Topic:** D.06. Vision

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**Title:** Dynamic correlated activity in vivo reveals rapid compensatory plasticity

**Authors: *A. ANDREI**[1], A. AKIL[2], N. KHARAS[1], R. ROSENBAUM[3], K. JOSIC[2], V. DRAGOI[1];
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**Abstract:** To produce adaptive behavior, capable of both learning and memory, neural networks must balance between plasticity and stability. Computational work has demonstrated that network stability requires plasticity mechanisms to be counterbalanced by rapid compensatory processes. However, such processes have yet to be experimentally observed. Here, we demonstrate that repeated optogenetic activation of excitatory neurons in visual cortex (area V1) in macaque monkeys induces a population-wide dynamic reduction in the strength of neuronal interactions over the timescale of minutes during the awake state, but not during sleep. This novel form of rapid plasticity was observed only in the correlation structure but not firing rates, which remained stable across trials. A balanced computational network model confirmed experimental findings and revealed that inhibitory plasticity is responsible for the decrease in correlated activity in response to repeated light stimulation. Changes in I-E connectivity was then confirmed experimentally. These results provide the first evidence for rapid homeostatic plasticity that primarily operates during wakefulness, which stabilizes neuronal interactions during strong network co-activation, counteracting fire-together wire-together mechanisms.

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**Poster**

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**Topic:** D.06. Vision

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National Natural Science Foundation of China (31930053)

**Title:** The neuronal mechanisms of visual perceptual learning in human early visual cortex: An intracranial electroencephalogram study

**Authors: *G. CHEN**, Q. WANG, F. FANG;
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**Abstract:** Training on simple perceptual tasks can lead to improved behavioral performance, which is referred to as perceptual learning. Perceptual learning is a key experimental paradigm for studying the plasticity of the brain, especially the visual system. The early visual cortex is generally thought to be involved in visual perceptual learning, whereas the characteristics of training-induced neural mechanisms in human early visual cortex have yet to be revealed. In the current study, we use high spatio-temporal resolution intracranial electroencephalogram (iEEG) technology to investigate the neuronal mechanisms of visual perceptual learning in human early visual cortex (V1, V2, and V3).We recorded iEEG signals from ten patients (four females) with drug-resistant epilepsy implanted with stereo-electrodes while they simultaneously learned to perform an orientation discrimination task for three days. The subjects showed substantial behavioral improvement in the trained orientation after three days of training. We identified a total of 84 visually responsive contacts in the early visual cortex (V1, n = 43; V2/V3, n = 41) that showed robust high-gamma activities (HGAs) to visual stimuli. All V1 contacts showed augmented HGAs to the trained orientation after training in both early (0 to 200 ms) and late (200 to 400 ms) response windows, while in V2/V3 contacts, augmented HGAs were only found in the late response window. Interestingly, training also led to a reduction of HGAs to the untrained orientation, in both V1 and V2/V3 contacts. Besides, by calculating the pairwise Granger causality index in each subject, we observed increased feedforward connections from V1 to V2/V3 after training, whereas the feedback connections from V2/V3 remained unchanged. Further analysis showed that, relative to the response to the untrained orientation, the response to the trained orientation nearly unanimously increased after training across all V1 and V2/V3 contacts, whether they preferred the trained or untrained orientation at the single-contact level before training. Another seven patients (three females) enrolled in the control group without training, and none of the above findings were present in the control group.
In summary, our study revealed several training-induced electrophysiological changes in human early visual cortex, which provide new evidence for the key role of human early visual cortex in visual perceptual learning.

**Disclosures: G. Chen:** None. **Q. Wang:** None. **F. Fang:** None.

**Poster**

**PSTR027. Plasticity of the Visual System in Health and Disease**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR027.09/Z10

**Topic:** D.06. Vision

**Support:** This work was supported by the Intramural Research Program of the National Institute of Mental Health (ZIAMH002966; NCT00001360).

**Title:** Patients with V1 damage exhibit orientation decoding in hMT+ after visual training

**Authors: *T. LIU**[1], M. CAVANAUGH[2], H. BACHMANN[1], B. K. FAHRENTHOLD[2], M. MELNICK[2], S. JAPEE[1], K. R. HUXLIN[2], E. P. MERRIAM[1];
[1]Lab. of Brain and Cognition, NIH, Natl. Inst. of Mental Hlth. (NIMH), Bethesda, MD; [2]Univ. of Rochester, Rochester, NY

**Abstract:** Orientation selectivity is a core property of primary visual cortex (V1) in mammals, yet patients with V1 damage can relearn to discriminate orientation at trained, blind-field locations. What neural machinery gives rise to orientation selectivity in V1-damaged patients? Here, we explore 2 possible mechanisms involving plastic changes in: 1) perilesional V1 and 2) pathways that bypass V1 and transfer information directly to extrastriate cortex, which may then use this input to construct orientation-selective signals. We studied 2 stroke patients (age: 45 & 63 years, 2 females). One patient had a large lesion in right V1 that resulted in a left homonymous hemianopia. The other patient had a lesion in right V2/V3 that spared V1, but resulted in left homonymous quadrantanopia. We also studied 2 age- and gender-matched controls. Subjects were scanned with BOLD fMRI while performing a demanding task at fixation and viewing task-irrelevant gratings in the periphery. Stimuli consisted of small (2.5 deg radius), oriented (45° or 135°), sinusoidal gratings, presented peripherally (7.1-8.6 deg eccentricity), either deep in the blind field or at a mirror-symmetric location in the intact visual field. Each subject also underwent additional imaging for retinotopic mapping, an MT localizer (moving vs. static dots), and T1-weighted structural scans. We first asked whether hMT+ was visually responsive in the absence of V1. All subjects had reliable responses in hMT+ (defined by a cortical atlas) to both full-field, moving dot stimuli, and to grating patches presented in the blind field, consistent with earlier studies showing that MT retains activity after V1 damage, presumably through circuits that bypass V1. We next evaluated orientation selectivity in hMT+. In the patient with a large V1 lesion, we could decode grating orientation from hMT+, but not from earlier cortical areas. In the patient with a V2/V3 lesion that spared V1, we could only decode orientation from V1, but not from hMT+. Control subject data revealed reliable orientation decoding in V1 but much weaker decoding in hMT+. Our findings suggest that after V1 damage, orientation selectivity seems to emerge from circuits that bypass V1 and project to MT, likely via koniocellular layers of the lateral geniculate nucleus and/or via the pulvinar. When V1 is spared, these alternative circuits do not generate strong orientation-selective BOLD signals in hMT+. This double dissociation raises intriguing questions about the mechanisms underlying plasticity for low-level visual features within the residual, adult visual circuitry after loss of a key processing node.

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**Poster**

**PSTR027. Plasticity of the Visual System in Health and Disease**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR027.10/Z11

**Topic:** D.06. Vision

**Support:** NEI/OBSSR Grant R01 EY027314
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NEI/OBSSR Grant R01 EY027314-05S2
Unrestricted Grant from Research to Prevent Blindness

**Title:** Early differential effects of V1 stroke on motion and orientation discrimination in humans

**Authors: *M. CAVANAUGH**[1], B. K. FAHRENTHOLD[1], J. YANG[1], B. REDMOND[1], D. TADIN[2], K. R. HUXLIN[1];
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**Abstract:** Ischemic damage to primary visual cortex (V1) causes devastating vision loss in the contralateral hemifield. Yet, we recently discovered that this loss is not immediate and absolute, with preserved, conscious direction discrimination inside a small proportion of perimetrically-defined blind fields <3 months post-stroke (E Saionz et al., 2022; *Brain*). Given the close functional links between orientation and direction processing (J Moon et al., 2022; *Psychonomic Bulletin and Review*), we now ask if patients with preserved motion discrimination also have preserved static orientation discrimination abilities.Fine direction discrimination thresholds were measured using random dot stimuli and controlled fixation in 25 subacute stroke patients as part of an ongoing clinical trial (NCT04798924). Fine, static orientation discrimination thresholds were measured using 100% contrast Gabors tilted left or right of vertical.Preserved direction discrimination within the blind field was detected in 7/25 patients, 3 of whom were further assessed for orientation preservation. None of these 3, nor the remaining 18 patients tested were able to discriminate orientation above chance. Patient age, deficit size, and sex ratios were equivalent between preserved and non-preserved patients. In contrast, preserved patients were found to be earlier post-stroke (2.5+/-1.1 months) than non-preserved patients (3.9+/-0.8 months; unpaired t-test, $p = 0.005$). This prompted us to investigate differences in retrograde degeneration as a possible substrate. Optic tract integrity was assessed with structural MRI, and integrity of the retinal ganglion cell complex was assessed with OCT. A laterality index (LI) was calculated for both to quantify shrinkage relative to structures subtending intact vision. While optic tract LI was similar between groups, there was significant inner retinal thinning in non-preserved patients relative to those with preserved blind-field motion abilities (unpaired t-test, $p = 0.009$). Our findings provide new evidence about the motion specificity of conscious discrimination abilities after V1 damage in humans, and suggests a neural substrate that survives early post-stroke, is evident at the level of the retina, but degenerates over time. Ongoing studies seek to determine if this preserved ability can be boot-strapped to enhance efficacy of training interventions, and to define neural substrates of perceptual training approaches that recover both motion and orientation discrimination in cortically-blinded fields.

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**Poster**

**PSTR027. Plasticity of the Visual System in Health and Disease**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR027.11/Z12

**Topic:** D.06. Vision

**Support:** ERC Grant 802482

**Title:** Perceptual learning improves fine orientation representation in macaque visual cortex as revealed by multi-voxel pattern analysis

**Authors: *B. KARAMI**[1,2], C. M. SCHWIEDRZIK[1,2];
[1]German Primate Ctr., Göttingen, Germany; [2]European Neurosci. Inst., Göttingen, Germany

**Abstract:** The visual system is equipped with a powerful plasticity mechanism, perceptual learning (PL), which serves to improve perception. However, the neural underpinnings of PL remain a matter of debate. Plasticity could act on representations within visual cortex, and/or enhance information transmission to and read out by downstream areas. A critical test of the former hypothesis is that plastic changes in neural representations should also persist in the absence of a task. Here, we test this prediction by tracking orientation information before and after learning through multi-voxel pattern analysis (MVPA) in macaque visual cortex during passive viewing.We acquired blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) activity in one male adult macaque monkey at two time points: before and after learning fine orientation discrimination. During scanning, we presented full-field Gabor gratings (6 orientations) in a block design. We trained a support vector machine (SVM) classifier on BOLD activity patterns of V1, V2, V3, V4, and TEO. Average decoding accuracies were 60% (*SD* 0.06) for V1, 62% (*SD* 0.06) for V2, 59% (*SD* 0.07) for V3, 56% (*SD* 0.08) for V4, 58% (*SD* 0.06) for TEO, and 62% (*SD* 0.05) for all visual areas combined. Decoding was statistically significant against baseline in all areas before training (all $p<10^{-6}$, corrected for multiple comparisons), except in V4 ($p=0.37$, corrected for multiple comparisons). After training, orientation decodability was significantly enhanced in all tested areas (all $p<10^{-4}$, corrected for multiple comparisons), especially in V4 ($p=0.007$, interaction time point × area $p=0.003$). Together, these results show 1) that fine orientation information is decodable from macaque visual cortex using MVPA, and 2) that PL can lead to long-term plastic changes of neural representations even at the absence of a task. This study thus reveals hitherto unexplored orientation information in MVPA of the macaque visual cortex and posits that PL may change neural representational spaces more permanently than previously thought.

**Disclosures: B. Karami:** None. **C.M. Schwiedrzik:** None.

**Poster**

**PSTR027. Plasticity of the Visual System in Health and Disease**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR027.12/Z13

**Topic:** D.06. Vision

**Support:** National Science and Technology Innovation 2030 Major Program (2022ZD0204802)
National Natural Science Foundation of China (31930053)

**Title:** Persistent Changes in Neural Dynamics and Connectivity through Extensive Training in Visual Motion Discrimination: An MEG Study

**Authors: *Y. SONG**, Q. WANG, F. FANG;
Peking Univ., Beijing, China

**Abstract:** Visual perceptual learning serves as a window into the study of brain neural plasticity. However, the limited spatial resolution and signal-to-noise ratio of EEG, along with the limited temporal resolution of fMRI, restrict our exploration of neural mechanisms underlying perceptual learning. Here, we utilized magnetoencephalography (MEG) technology to record high temporal-resolution neural signals from subjects who underwent extensive training in a visual motion direction discrimination task for eight days. We measured their behavioral performance and recorded MEG signals before (Pre), immediately after (Post1), and two weeks after training (Post2). After training, we observed long-lasting behavioral improvement at the trained direction. Based on MEG signals from occipital sensors, we built time-resolved classifiers to decode motion directions. Training significantly reduced the latency in the decoding time course and strongly increased the decoding accuracy. Notably, peak decoding accuracies were negatively correlated with behavioral thresholds. Further, we employed a time-resolved multivariate inverted encoding model (IEM) to track the ongoing time courses of direction-specific neural representations of motion stimuli. By decomposing and reconstructing the neural signals, we showed that training enhanced the direction-selective responses and increased the representation fidelity at the trained direction. Importantly, none of the above changes was found at untrained directions. Moreover, our Granger Causality Analysis, following MEG source reconstruction, indicated that training strengthened the feedforward connection from early visual cortex (EVC) to V3A.Taken together, our study provides evidence that extensive training modifies early-stage neural responses and feedforward connections in visual processing, shedding new light on the neural basis for behavioral performance enhancements.

**Disclosures:** **Y. Song:** None. **Q. Wang:** None. **F. Fang:** None.

**Poster**

**PSTR027. Plasticity of the Visual System in Health and Disease**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR027.13/Z14

**Topic:** D.06. Vision

**Support:** NIH NEI Grant 1R01EY031589-01
NIH NEI Grant U01EY025858

**Title:** Functional connections of discrete cortical regions defined based on individuals' experiences are plastic and individual-specific

**Authors: *P. DEMIRAYAK**[1], R. CHUA[1], L. L. FLEMING[2], K. M. VISSCHER[1]; [1]Neurobio., Univ. of Alabama At Birmingham, Birmingham, AL; [2]Mclean Hospital/Harvard Med. Sch., Mclean Hosp./Harvard Med. Sch., Atlanta, GA

**Abstract:** While the functional connectivity patterns in the adult brain have been well investigated, quantitative study of individual-specific plasticity in functional connectivity have been more limited. We examine this in people with late stage Macular Degeneration (MD). These patients lose the sensory receptors for central vision and often use locations in peripheral vision for daily tasks requiring vision. Because of the retinotopic organization of early visual areas, different parts of the cortex experience sensory deprivation and increased usage. Two participants with similar sensory loss may develop individual-specific neural strategies for adaptation to vision loss. Our aim is to examine experience-dependent plasticity in functional connections for the deprived area of cortex (lesion projection zone, LPZ), an area of increased use (the preferred retinal locus (PRL), and a control region (unpreferred retinal locus, URL) corresponding to areas in V1 in individuals with MD. We performed seed-to-voxel analyses (fingerprints) from the cortical correspondence of LPZ, PRL, and URL in 21 MD and 23 control participants. This allowed us to examine how 'typical' the whole-brain functional connection pattern is for each participant, that is, how similar the pattern is to that of a typical healthy vision control. Given that LPZ and PRL experienced different usage in MD participants, we hypothesized that their cortical representations would have less typical fingerprints in MD participants than in controls. Our approach also allowed a within-subject control, as we expect no difference for the URL. Our results indicated that both LPZ and PRL fingerprints are less typical in MD than control. Further, within the MD participants, LPZ and PRL fingerprints are less typical than URL fingerprints, showing within-subject effects. We also assessed LPZ and PRL fingerprint similarities to compare increased vs decreased usage of the retinal regions. In MD patients, the PRL fingerprints were less typical than the LPZ fingerprints, whereas this difference was less pronounced within the control group. These findings support the idea that functional connections from V1 maintain the capacity to adapt in the adult brain and that these adaptations may be idiosyncratic to the individual's experiences.

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**Poster**

**PSTR027. Plasticity of the Visual System in Health and Disease**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR027.14/Z15

**Topic:** D.06. Vision

**Support:** NIH R01 EY033835
NIH R21 EY030588
Stanford Wu Tsai Big Idea and Accelerator Grants: Neurodevelopment Initiative

**Title:** Structural development of early emerging sulcal folds in humans during the first year of infancy

**Authors:** *S. TUNG[1], ***S. TUNG**[2], X. YAN[6], B. FASCENDINI[2], C. M. REYES[2], K. DUCRE[2], K. PEREZ[2], A. ALLEN[2], J. HORENZIAK[2], H. WU[3], V. NATU[2], K. GRILL-SPECTOR[2,4,5]; [1]Stanford Univ., Campbell, CA; [2]Psychology, [3]Ctr. for Cognitive and Neurobiological Imaging, [4]Neurosciences Program, [5]Wu Tsai Neurosciences Inst., Stanford Univ., Stanford, CA; [6]Inst. of Sci. and Technol. for Brain-Inspired Intelligence, Fudan Univ., Shanghai, China

**Abstract:** During fetal development, sulci emerge at different time-points. The earliest emerging sulci are more spatially consistent, better predict functional regions, and are hypothesized to be under closer genetic control than later developing sulci. However, it is unknown how anatomical features of the earliest emerging sulci develop in the first year of human life. By combining structural and quantitative MRI, we longitudinally examined the development of sulcal depth, cortical thickness, and tissue microstructure ($R_1$ relaxation rate) of the earliest emerging sulci in human infants across four timepoints ($N_{newborn}$= 27, 10 females, $Mean_{age}$ ± SD: 29.1 ± 9.92 days; $N_{3\text{-}months}$= 27, 14 females, 105.8 ± 18.63 days; $N_{6\text{-}months}$ = 20, 10 females, 189.3 ± 15.82 days; and $N_{12\text{-}months}$= 4, 2 females, 376.0 ± 16.43 days). Higher $R_1$ indicates higher tissue density and a more developed cortex. We focus on 12 major sulci that emerge *in utero* between 16 - 31 gestational weeks, for their stability and consistency across infants. We used cortex-based alignment to align each sulcus, drawn on the adult average FreeSurfer cortical sheet, onto each individual infant's brain. The reliability of automated sulcal fold mapping was validated by comparing the accuracy of automated versus hand-drawn sulci using dice coefficients. Our data reveal four main findings. First, from birth to one year of life, we find significant increases in mean sulcal depth of all sulci, except for the calcarine sulcus. Surprisingly, sulci that emerge early in gestation are deeper at birth than later emerging sulci, but deepen after birth more slowly than later emerging sulci. Second, 9/12 of these sulci significantly thicken from birth to 12 months of age, except for the calcarine, central sulcus, and lateral occipital sulcus. Sulci that emerge earlier are also thicker at birth than later emerging sulci but develop more slowly than later emerging sulci. Third, all 12 sulci show significant increases in $R_1$ from birth to 12 months of age, illustrating profound microstructural cortical growth after birth. Finally, using linear mixed models, we tested if development of $R_1$ and/or thickness predicts sulcal deepening and find that $R_1$ alone better predicts sulcal depth in infants as compared to $R_1$ and thickness combined. Together, these findings suggest that differential changes in sulcal depth may be associated with the development of cortical tissue properties in the first year of human life.

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**Poster**

**PSTR027. Plasticity of the Visual System in Health and Disease**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR027.15/Z16

**Topic:** D.06. Vision

**Support:** Stanford Wu Tsai Neurosciences Institute Accelerator Grant
NIH R01 EY033835
NIH R01 EY022318

**Title:** Distribution of iron and myelin in basal ganglia and primary sensory cortices from infancy to adulthood

**Authors: *V. NATU**[1], X. YAN[2], H. WU[3], S. TUNG[1], B. FASCENDINI[1], K. GRILL-SPECTOR[1];
[1]Psychology Dept., Stanford Univ., Stanford, CA; [2]Inst. of Sci. and Technol. for Brain-Inspired Intelligence, Fudan Univ., Shanghai, China; [3]Ctr. for Cognitive and Neurobiological Imaging, Stanford Univ., Stanford, CA

**Abstract:** Iron is an essential metal and micronutrient for brain health and generation of cortical myelin. It is well established that iron deficiency can lead to cognitive impairments like autism and motor learning difficulties in childhood. However, the role iron plays in typical human brain development postnatally remains largely unknown. By combining quantitative susceptibility mapping, effective transverse relaxation rate ($R_2$*[$s^{-1}$]) and longitudinal relaxation rate ($R_1$[$s^{-1}$]) in 14 infants (age range: 16-479 days) and 10 adults (23-42 years), we tracked the distribution of iron and myelin in subcortical basal ganglia (BG) nuclei and gray and white matter (WM) tissue of primary sensory-motor areas (M1, S1, A1, and V1). Higher $R_2$* and $R_1$ values are linearly related to higher iron content and higher tissue density, respectively. Our data reveal three main findings: First, in BG nuclei and primary sensory-motor areas, there are linear increases in $R_2$* and $R_1$ with log10(age). However, $R_2$* and $R_1$ increase faster in BG nuclei than in primary sensory-motor areas, suggesting differential changes in tissue properties across the brain during development. Further, magnetic susceptibility ($\chi$) reveals more paramagnetic (iron-like) properties in adult than infant BG nuclei, but diamagnetic (myelin-like) properties in sensory cortices across ages. Second, we estimated the contribution of iron ($C_{Fe}$) and myelin ($C_{My}$) from $R_2$* and $\chi$ using empirical linear models[1] (Eqs. 1 and 2), estimated iron levels from a prior postmortem study[2], and a least square solver: Eq1: $R_2^*(c_{Fe}, c_{My}) = a_{Fe} * c_{Fe} + a_{My} * c_{My} + a_0$; Eq2: $\chi(c_{Fe}, c_{My}) = b_{Fe} * c_{Fe} + b_{My} * c_{My} + b_0$. $C_{Fe}$ maps resemble $R_2$* maps, consistent with the idea that $R_2$* is a better proxy for iron than myelin. $C_{My}$ maps are more similar to $R_1$ than $R_2$* maps in primary sensory areas, further highlighting the dominant role of iron in $R_2$* contrast. Third, we tested how $R_2$* and $R_1$ vary as a function of cortical depth in primary sensory areas. In adults, $R_2$* and $R_1$ both increase from cortex to WM, illustrating a corresponding relationship between iron and myelin cortical profiles. In newborns, however, both $R_2$* and $R_1$ are higher in cortex than in WM and this pattern reverses around 3 months for $R_1$ and around one year for $R_2$*,

suggesting differential iron and myelin profiles during infancy. Together, our results pave the way to estimate concentrations of iron and myelin in infant brains from in vivo measurements, which is critical for establishing global standards to identify iron deficiency in the brains of developing infants and provide effective postnatal care. **References:** 1] Stüber, C., et al. (2014). *Neuroimage.* 2] Hallgren, B., & Sourander, P. (1958). *J. of Neurochem.*

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**Poster**

**PSTR027. Plasticity of the Visual System in Health and Disease**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

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**Topic:** D.06. Vision

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MG: T32GM081760
MB: P30 CORE award EY08098
MB: Eye & Ear Foundation of Pittsburgh
MB: The Research to Prevent Blindness Inc, NY
SR: NSF GRFP DGE2140739

**Title:** Plasticity of hemispheric functional organization after pediatric epilepsy surgery

**Authors: *S. ROBERT**[1], M. C. GRANOVETTER[2,3], C. PATTERSON[4], M. BEHRMANN[5]; [2]Dept. of Psychology and Neurosci. Inst., [1]Carnegie Mellon Univ., Pittsburgh, PA; [3]Dept. of Med., [4]Dept. of Pediatrics, [5]Dept. of Ophthalmology, Univ. of Pittsburgh, Pittsburgh, PA

**Abstract:** Children, but not adults, often maintain or regain cognitive functioning after extensive cortical damage. The mechanisms underlying this capacity remain poorly understood. Plasticity in childhood might allow functional remapping or compensation through changes in functional connectivity between brain areas distal to the epileptogenic zone, i.e., the intact hemisphere. In this study, we recorded BOLD responses from patients with drug-resistant epilepsy after large cortical resections (n = 14, 7 left and 7 right affected hemispheres, age range: 7-37, n = 6 male) and controls (n = 36, age range: 9-32, n = 22 male) as they viewed and listened to an 11-minute segment of a movie in an fMRI scanner. To examine functional connectivity at the hemisphere level, we parcellated the intact hemisphere of the patients and both hemispheres of the controls into 180 parcels using an anatomical atlas (Glasser et al., 2016) and calculated all pairwise statistical dependencies (Anzellotti et al., 2017). We further sorted the edges between the 180 parcels into edges belonging to 22 networks and further into edges between 8 large-scale regions to determine whether reorganization is more likely to emerge at a certain level in the hierarchy of networks in the brain. For each patient group (intact left or right hemispheres), we assessed the statistical dependencies of the entire hemisphere connectivity, the connections within and

between networks, as well as specific edges, against controls at each network level using inter-subject correlation analysis and linear mixed effects modelling. Three main results emerged: 1) the intact hemisphere connectivity profiles of both patient groups differed significantly from controls, suggesting reorganization of the relative distribution of strong connections in both hemispheres, 2) global measures of within- and between-network connectivity were preserved in the left hemisphere intact group but reduced in the right hemisphere intact group, and 3) at the more local level, right hemisphere intact patients had widespread reductions in connectivity while differences in the left hemisphere intact patients were sparse and in both directions. These findings reveal the specificity in the connectivity changes following cortical resection. The large-scale reorganization of networks in the intact, preserved hemisphere might reflect emergent plasticity in the service of maintained and/or retained cognitive function.

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**Poster**

**PSTR028. Processing of Contrast, Form, and Color**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR028.01/Z18

**Topic:** D.06. Vision

**Title:** Sparse Linear Discriminant Analysis of fMRI Responses to Colored Gratings Reveals Signatures of Visual Areas, Eccentricity, and Upper-Lower Visual Field Asymmetries

**Authors: *S. DUFFIELD**[1], S. LOGGIA[2], K. BRAUNLICH[3], B. R. CONWAY[4];
[1]NIH, Natl. Eye Inst. (NEI), Decatur, GA; [2]NIH, Brattleboro, VT; [3]NIH, Dickerson, MD; [4]Natl. Inst. of Hlth., Bethesda, MD

**Abstract:** Visual perception in primates depends on many regions of the cerebral cortex, including a series of retinotopically organized areas (V1, V2, V3). What computational objective is carried out by the retinotopic organization—by the division into hemifield (upper versus lower visual field), by eccentricity (fovea versus periphery), and by visual area (V1, V2, V3, V4)? To address these questions, we measured fMRI responses in two alert macaque monkeys trained to fixate a screen on which we displayed gratings that varied in spatial frequency, color, and saturation. We also obtained data in the same animals using retinotopic mapping stimuli that allowed us to parcellate the visual cortex by hemifield, eccentricity, and area. We analyzed the data with a novel variant of sparse linear discriminant analysis (sLDA) that discovers a combination of stimulus features that best separate the retinotopically defined parcels. Fitting the model to responses constrained only by each voxel's eccentricity preference uncovered a single component (reflecting responses to a combination of stimuli) that separates cortical fields by their eccentricity preference, from fovea to periphery. This component maps onto expected dimensions that govern eccentricity representations, namely spatial frequency and S-cone response. We then fit the model to voxel responses considering each voxel's dorsal/ventral

representation and retinotopic area. The model discovered two components. The first separated dorsal/ventral subdivisions of all areas, and the second separated retinotopic areas according to their location in the putative visual processing hierarchy. Ventral regions compared to dorsal regions were characterized by increased response to colors associated with natural daylight (orange/blue) and decreased response to luminance contrast. Meanwhile, earlier visual regions (V1) compared to later visual regions (V4) were characterized by greater responses to contrast and saturation. Interestingly, the separation of dorsal and ventral subdivisions by component 1 was progressively larger for increases in component 2 (from V1 to V4). These results may resolve persistent debate concerning V4: known asymmetries in the response properties of the candidate dorsal/ventral subdivisions have encouraged an hypothesis that these candidate subdivisions are not part of the same visual area. The present work suggests they are part of the same area, and that they inherent and amplify their asymmetries from biases evident in V1. Taken together, these results and analysis show that sLDA is a powerful data-driven tool for discovering hypotheses about cortical function and behavior.

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**Poster**

**PSTR028. Processing of Contrast, Form, and Color**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR028.02/Z19

**Topic:** D.06. Vision

**Title:** Color categories in macaque monkey and their sources

**Authors: *D. J. GARSIDE**, H. M. SELWYN, A. L. Y. CHANG, B. R. CONWAY;
NIH, Natl. Eye Inst. (NEI), Bethesda, MD

**Abstract:** Categorization and memory are hallmarks of cognition, often studied with color, a controllable, continuous variable of behavioral relevance. One question has been the extent to which categorization and memory are impacted by language. The question has been challenging to answer, not only because all cultures have language, but also because sets of colors used to assess categorization and memory are defined by color spaces assumed to be perceptually uniform, an assumption known to be only approximate. Macaques, who have the same cone types and a similar cortical organization as humans but obviously lack language, provide an opportunity not only to assess these behaviors in the absence of language, but also to evaluate assumptions about the perceptual uniformity of color spaces. Four macaque monkeys were tested in multiple weekly sessions over several years (~220,000 trials) in an alternative forced-choice color-matching task adapted from a study of humans in which systematic errors in color matches provide a metric of color categories (Bae et al., J Exp Psychol Gen, 2015). The macaques learned to perform the task at above chance levels within ~5000 trials and plateaued at ~85% accuracy (chance = 25%) for the easiest color discriminations within ~30,000 trials. The data were fit with a mixture model where errors are a mixture of guessing and noisy memory. The analysis shows a

common pattern of errors across the four animals, consistent with two color categories. These line up with human designations of warm (hue angle = 13° in CIELUV, SD = 17°) and cool (hue angle = 210° in CIELUV, SD = 13°). Some of the monkeys also showed additional idiosyncratic pattern of errors, stable over time, providing evidence of individual differences in color categorization. We next asked about the underlying causes of the errors. One possibility is that they have a cognitive origin; another possibility is that they reflect unrecognized non-uniformities in the presumed uniform color space. These possibilities cannot be distinguished by a mixture model but we show they can be distinguished with a modification of the "target confusability competition model" (Schurgin et al., Nat Hum Behav, 2020). The analysis shows that the pattern of errors common to all four animals are best explained by a previously unrecognized non-uniformity in color space (delta-Akaike Information Criterion = $2x10^3$), while the individual differences appear to have a cognitive origin. Finally, we used the monkeys' behavioral results to estimate the non-uniformities, to reconstruct a color space that is perceptually uniform and uncontaminated by language.

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**Poster**

**PSTR028. Processing of Contrast, Form, and Color**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR028.03/Z20

**Topic:** D.06. Vision

**Support:** NIH Grant EY018849

**Title:** Color and luminance processing in V1 complex cells and artificial neural networks

**Authors: *L. BUN**, G. HORWITZ;
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**Abstract:** Luminance and chromatic light edges play critical roles in human vision. In primary visual cortex (V1), edges are encoded by simple and complex cells. Some simple cells encode luminance edges and others encode chromatic edges. Simple cell outputs are received by complex cells. Some complex cells are sensitive to both luminance and chromatic edges, while others are only sensitive to luminance edges. None are only sensitive to chromatic edges. The reason why the color tuning distribution of complex cells differs from the simple cells that underlie them is not immediately obvious. One possibility is that the color tuning of complex cells facilitates efficient object recognition in natural images. To test this hypothesis, we experimented on convolutional neural networks (CNNs) trained for object recognition. Because CNNs perform a single task, any features we observe are likely useful for that task. We replicated previous V1 experiments on six CNNs that span a wide range of architectures and were all trained to recognize objects in the ImageNet dataset. We presented these CNNs with

colorful grating stimuli and analyzed collections of stimuli that drove a common response from individual units. The colors of these "isoresponse stimuli" are represented in a three-dimensional color space where each axis represents the value of a color channel. In this space, isoresponse stimuli form surfaces that provide clues to the computations that units perform. We focused on the isoresponse surfaces of CNN units that were invariant to the phase of the grating stimuli, making them analogous to V1 complex cells. These surfaces are similar to surfaces associated with V1 complex cells. Some surfaces were ellipsoidal or hyperbolic, similar to those associated with complex cells jointly sensitive to luminance and chrominance. Other surfaces were planar, indicating sensitivity to a single color direction orthogonal to the plane. All planar surfaces were orthogonal to luminance. Thus, like V1 complex cells, all complex units sensitive to one color are sensitive to luminance. These observations are consistent with the idea that a subset of V1 complex cells and CNN units combine luminance and chrominance in a manner that is well suited for object recognition. The paucity of purely chromatic complex cells in V1, and their counterparts in CNNs, suggests that such signals are relatively unhelpful for object recognition. These results provide valuable insight into the mechanisms underlying human visual perception.

**Disclosures: L. Bun:** None. **G. Horwitz:** None.

**Poster**

**PSTR028. Processing of Contrast, Form, and Color**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR028.04/Z21

**Topic:** D.06. Vision

**Support:** NSFC 31822023
NSFC 31871053

**Title:** Neural Code of Object and Illuminant Color in the Ventral Visual Pathway

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**Abstract:** Our visual system provides a robust representation of object category, identity, and object-related features. One of the major challenges for our brain is the extraction of the object's surface color independent of the illumination color, known as the "color constancy" problem. It remains unclear how the visual system dissociates the confounding information and computes the color of the object. In the present study, we investigated the neural code of object color at different stages of the macaque ventral visual pathway and examined the extent to which object color is encoded with the dissociation of other confounders in the color selective areas. We presented realistic object models with different object colors (i.e., the reflectance) in the 3D scene rendered under different color illuminants, and we recorded single-neuron responses to these stimuli in V4, PLC (posterior lateral color patch) and ALC (anterior lateral color patch) in

the inferotemporal cortex. Along the ventral visual hierarchy, there was an increase in the representation of object color from V4 to PLC, to ALC, and a group of ALC neurons represent the object color invariant to illuminant changes. Furthermore, we observed strong representations of object shape and position in PLC, which are often mixed with the representation of object color in a gain-modulated manner. The representation of shape and position and their interactions with color information were much weaker in ALC. This suggests that the object color and other properties are still entangled in PLC, but are dissociated in ALC, so that the representation of object color is more condition-general in ALC. Our results reveal the neural code of object color in a more realistic and complex situation across the ventral visual pathway, and provide insights into the dissociation of object color and other confounding factors in the color selective areas.

**Disclosures: G. Zhang:** None. **L. Chang:** None.

**Poster**

**PSTR028. Processing of Contrast, Form, and Color**

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**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR028.05/Z22

**Topic:** D.06. Vision

**Support:** NSF IOS 2026334

**Title:** Visual pattern preferences: Testing the processing bias hypothesis with background-matching stimuli to shed light on signal design evolution

**Authors: *Y. HEJJA BRICHARD**[1], M. RAYMOND[2], I. C. CUTHILL[3], T. C. MENDELSON[1], J. P. RENOULT[4];
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**Abstract:** The diversity of sexual signals is thought to arise in part from conflicts between natural and sexual selection. Sexual selection favors conspicuousness and can arise from animal mate preferences whereas natural selection penalizes detectability to avoid predators. Evolutionary trade-offs to address this conflict are a common explanation for sexual signal diversity. The processing bias hypothesis (Renoult & Mendelson 2019) suggests that signals evolve to exploit perceptual biases for both effective and efficient information processing, which suggests that natural and sexual selection may not be in conflict for animal patterns. Indeed, one strategy to reduce detectability is background matching, yet, human studies suggest that background matching could also be visually attractive, as people tend to prefer images that match the statistics of natural scenes. This preference derives from an adaptation of sensory systems to efficiently process those natural statistics. The processing bias hypothesis predicts that once detected, camouflage patterns should also be attractive. This is an important and untested prediction suggesting that camouflage could serve as an evolutionary precursor of

sexual signals. Here, using humans as an animal model, we test whether camouflage patterns are intrinsically visually attractive. We first used a detection task to assess the camouflage effectiveness of patterned stimuli that varied in their background matching level. In a second and third task, we tested the attractiveness of those patterns, using the same stimuli as in task 1 but removing the detectability constraint by circling and centering the targets. Stimuli were presented either against a gray background to assess the baseline attractiveness of the target stimuli (task 2) or against the same patterned backgrounds as for the detection task (task 3). Preferences were assessed using a two-alternative-forced-choice design. A total of 1757 participants completed our online study, with each participant completing the detection task and one preference task, in a random order. As predicted, we found that the most effectively camouflaged stimuli (detection task) were also the most attractive stimuli when rendered detectable. We further found that the absolute preference peak is also aligned with the average statistics of natural scenes and that a patterned background modulates those preferences. Our results support the hypothesis that camouflage patterns possess intrinsic visual attractiveness. This suggests that natural and sexual selection may share similar selection optima with camouflage potentially serving as an evolutionary precursor of sexual signals.

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**Poster**

**PSTR028. Processing of Contrast, Form, and Color**

**Location:** WCC Halls A-C

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**Topic:** D.06. Vision

**Support:** National Natural Science Foundation of China (31970927)

**Title:** Color saturation drives oscillatory responses in V4

**Authors: *H. CAO**[1,2], Y. LIU[1], J. YIN[3], Z. CHEN[1], Y. LIU[1,2], X. WANG[1,2], X. LI[1], Y. LU[1], I. ANDOLINA[1], N. MCLOUGHLIN[4], S. SHIPP[1], W. WANG[1,2];
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**Abstract:** Our visual world is rich in color information. The perception of color is commonly described in reference to three color dimensions: hue, saturation or chroma and value or lightness. With hue referring to the peak of the color spectrum, saturation (or chroma) referring to the spread of the color spectrum, and value (or lightness) referring to the overall intensity of the color spectrum. Previous psychophysical studies on humans have suggested that red (hue) stimuli and those with high saturation have a strong effect on arousal. Electrophysiological

studies conducted on both human and non-human primate visual cortices have demonstrated a red dominance in neural responses compared to other colors, but have done so without considering saturation levels. A more recent study looking in primate V1 found a significant effect of the background on responses. Since the gamma (γ) band is often associated with cognitive function such as attention and stimulus awareness in V4, we hypothesized that it might be the saturation of a colored stimulus that drives the power of gamma band activity in color perception rather than the hue of a stimulus. To test this hypothesis, we used linear depth probes to record local field potentials (LFP) and multi-unit activity (MUA) in V4, while presenting isoluminant color stimuli both within responsive fields (RF) and as full field stimuli. We calculated the power spectrum density (PSD) of the LFP signals to six isoluminant hues (red, orange, green, cyan, blue, purple) with varying saturation levels (color distance along the saturation axe of each hue is 0.02 DE in CIE Lu'v' color space, three to nine levels depending on the gamut). We found that color patches of all hues induced significantly higher power in both the γ-low (30-50Hz) and γ-high (50-100Hz) bands at higher saturation levels. Furthermore, when comparing different chromatic stimuli at the same saturation level, we observed no specific hue that exhibited a greater γ-band power response. In conclusion, high saturation color patches of all hues representing the chromaticity drive a significantly enhanced γ-band response. This increase in γ-band response does NOT depend on the hue of the colored stimulus but rather is dependent on the saturation of the color.

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**Poster**

**PSTR028. Processing of Contrast, Form, and Color**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR028.07/Z24

**Topic:** D.06. Vision

**Title:** Examining individual alertness in the novel short-term color light exposure paradigm: A pilot study.

**Authors: *A. LITOVCHENKO**;
UNC Charlotte, Charlotte, NC

**Abstract:** This study used a novel short-term drowsiness paradigm to investigate the effects of yellow and blue light exposure on drowsiness in a dimly lit environment using the Karolinska Sleepiness Scale (KSS). Thirty-two participants were randomly assigned to two groups, which underwent a 10-minute dark adaptation stage followed by two 10-minute colored light exposures. One group had blue followed by yellow light exposure, and the other followed the reverse path. The study hypothesized an increase in drowsiness after the dark adaptation stage, a rise in KSS scores over 30 minutes of the experiment, and a significant interaction between color

and order of light exposure. The results supported the first two hypotheses but not the third. There was a statistically significant increase in drowsiness levels after the dark adaptation stage, $t(31) = 3.003$, $p < .01$, two-tailed. There was an overall trend of the sleepiness measure to increase in a 30-minute experiment regardless of the light order exposure during the second and third stages of the investigation, $F(1,30) = 6.177$, $p = .019$, partial $\eta^2 = .171$. The hypothesis about the potential impact of the color order was rejected for this study due to its statistical insignificance. However, since the effects of yellow light exposure after dark adaptation were approaching significance, $t(15) = 2.097$, $p = .053$, it was concluded to investigate this phenomenon further in future studies. The findings suggest that various light colors can impact drowsiness levels, provide insights into the relationship between light exposure and drowsiness during the daytime, and highlight the importance of considering color order in future studies, contributing to the understanding of light exposure on human performance.

**Disclosures: A. Litovchenko:** None.

**Poster**

**PSTR028. Processing of Contrast, Form, and Color**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR028.08/Z25

**Topic:** D.06. Vision

**Title:** The emergence of individual colour-space geometries in the human brain

**Authors: *L. TEICHMANN**, D. GARSIDE, A. BENITEZ-ANDONEGUI, S. MONTESINOS, F. PEREIRA, C. BAKER, B. R. CONWAY;
NIH, Bethesda, MD

**Abstract:** Formal colour spaces capture similarity relationships based on behavioural data but there are discrepancies between these models and perception. Here, we collected Magnetoencephalography (MEG) data to test the extent to which these discrepancies can be accounted for by the neural representation of colour. Using a dense sampling of colour space, we recorded brain responses in humans evoked by hundreds of colours to measure how perceptual colour-space geometries unfold over time. Our stimuli varied in hue such that the entire hue circle was finely sampled, allowing us to model fine-grained differences in the neural response with millisecond temporal resolution. First, we used established approaches to test data quality and colour information at a coarse level. Specifically, we analysed eyetracking data to ensure central fixation, examined evoked responses across different colours and used time-resolved pairwise decoding to differentiate between broad colour categories. Second, we used an inverted encoding model with equally spaced tuning functions to associate MEG-sensor activity at each timepoint with distances between different hues in CIECAM02 colour space. Using independent MEG data, we then predicted stimulus colour from the neural data and assessed similarities and differences between the neural and behavioural representations of colour. In line with previous findings (e.g., Rosenthal et al., 2021, *Current Biology*; Teichmann et al., 2019, *NeuroImage*;

Teichmann et al., 2020, *JNeurosci*), our results show that colour information is present in the neural signal from ~100 ms onwards. However, we found that colour space geometries unfold in a non-uniform way. These findings demonstrate that continuous, multivariate predictors afford a high sensitivity to disentangle unique colour representations from MEG data. Our findings provide novel insights into how individual colour geometries emerge and unfold in the human brain.

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**Poster**

**PSTR028. Processing of Contrast, Form, and Color**

**Location:** WCC Halls A-C

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**Topic:** D.06. Vision

**Support:** NIH Intramural Program
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**Title:** The spatiotemporal structure of cone inputs to V1 receptive fields at the center of gaze

**Authors: *F. BARTSCH**[1], R. BARTOLO-OROZCO[2], E. J. LOTT[1], J. YATES[3], D. BUTTS[4], B. R. CONWAY[5];
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**Abstract:** Mechanisms in V1 that process retinal signals at the center-of-gaze (the fovea) underlie both high-acuity spatial vision and color vision. But knowledge of these mechanisms is limited, due to difficulty tracking the tiny eye movements that occur even when fixating. Such microsaccades can be on the same scale as the predicted size of foveal V1 receptive fields, approaching one arc minute. It has often been assumed that foveal V1 receptive fields are simply finer versions of parafoval receptive fields. Yet this assumption might not be valid given distinct anatomical, physiological, and behavioral characteristics of foveal vision, including higher cone density, precise cone sampling by retinal circuits, and overt attentional mechanisms. Non-foveal V1 neurons pool over many cones; it is an open question how the limited cone pooling of tiny foveal receptive fields determine how spatial and color vision are processed in V1.Here, we recorded neuronal activity from foveal V1 in alert fixating macaque monkeys using two chronic multielectrode arrays in one hemisphere and an acute laminar array inserted perpendicularly to the cortex in the other hemisphere. We elicited neural responses using spatio-chromatic noise defined in a physiologically defined cone-opponent color space which reflects the structure of color processing in lateral geniculate nucleus, and we used model-based eye tracking that used

the fine spatial structure of foveal RFs recorded across the chronic arrays to infer eye-position at the resolution of foveal V1 neurons. We then studied the spatial and chromatic processing of 389 V1 neurons sampled across cortical depth recorded across many foveal V1 positions using the acute laminar probe. We observed V1 spatio-chromatic RFs spanning as little as 6 arcminutes with fine-scale features measuring 1-2 arcminutes. Notably, these features were consistently finer when assessed for stimuli that combine across cone types (yielding luminance) than for stimuli that subtract cone types (yielding color). Even in cells strongly modulated by both luminance and color, the luminance subregions were on average 24% smaller than L-M or S subregions. Furthermore, stronger color modulation was generally associated with larger RF size. These results indicate a preferential encoding of high-resolution shape processing in foveal V1 through luminance signals. Our measurements offer the first detailed insights into the spatial-chromatic processing occurring in foveal V1 and begin to bridge the gap between retina and visual perception at the center of gaze.

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**Poster**

**PSTR028. Processing of Contrast, Form, and Color**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR028.10/Z27

**Topic:** D.06. Vision

**Title:** Contributions to visual and non-image forming behaviors from the M4 intrinsically photosensitive retinal ganglion cells

**Authors: *K. M. DALY**[1,2], C. BEIER[1], G. OSTERMEYER[3], J. LEFFLER[4], N. M. ALAM[5], W. N. GRIMES[6], G. T. PRUSKY[5], J. S. DIAMOND[6], B. SIVYER[4], L. BROWN[3], S. HATTAR[1]; [1]Natl. Inst. of Mental Hlth., Bethesda, MD; [2]Dept. of Biol., Johns Hopkins Univ., Baltimore, MD; [3]Dept. of Integrative Physiol. & Neurosci., Washington State Univ., Pullman, WA; [4]Dept. of Ophthalmology, Casey Eye Inst., Oregon Hlth. and Sci. Univ., Portland, WA; [5]Burke Neurolog. Inst., White Plains, NY; [6]Natl. Inst. of Neurolog. Disorders and Stroke, NIH, Bethesda, MD

**Abstract:** Environmental light detected by photoreceptors is transduced and ultimately integrated by retinal ganglion cells (RGCs), which relay visual information to the brain. Approximately 5% of these retinal ganglion cells are intrinsically photosensitive, able to directly detect blue light via the photopigment melanopsin and consequently signal downstream processes independent of rod and cone input. Importantly, ipRGCs contribute to visual processing and are key players in modulating the effect of light on numerous non-image forming processes such as circadian photoentrainment, mood, cognition, sleep, feeding, body temperature, and pupil constriction. The varied effects of ipRGCs on these behaviors is consistent with data demonstrating that ipRGCs are morphologically and physiologically diverse.

To better understand the influence of light on health, we aim to illuminate behavioral contributions of ipRGCs at a finer scale.
Improved cellular resolution in sequencing technologies has provided a method to further explore the heterogeneity of ipRGCs and their contributions to non-image forming processes. To date only a handful of genes are known to define subpopulations of ipRGCs. The first is the transcription factor *Brn3b*, whose lack of expression labels approximately 200 ipRGCs which are sufficient to drive circadian photoentrainment. Recent studies have also indicated that the genes *Tbx20* and *Rasgrp1* are differentially expressed among ipRGCs, although it's unclear whether expression of these genes define functionally or morphologically distinct subpopulations of ipRGCs and how they may impact behavior.
In this work, I analyze publicly available single cell sequencing atlases of the mouse retina to reveal a robust molecular signature for a morphologically distinct type of ipRGC known as the M4 (ON sustained alpha ganglion cell). I further identify M4 axon innervation to central targets associated with both visual and non-image forming behaviors via dual recombinase intersectional viruses. Finally with a combination of viral and genetic tools to intersectionally encode DREADD hM3D(Gq) or hM4D(Gi), I chemogenetically manipulate the M4 cell type to investigate its contribution to visual and non-image forming behaviors.
This work expands our knowledge of the M4 ipRGC beyond *ex vivo* retinal physiology and establishes a viable strategy to interrogate behavioral contributions of retinal cell populations based on a two-gene signature. To our knowledge this is the first study to isolate and investigate the impact of a classic ipRGC subtype *in vivo*.

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**Poster**

**PSTR028. Processing of Contrast, Form, and Color**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR028.11/Z28

**Topic:** D.06. Vision

**Title:** Factors governing cross-orientation suppression in macaque V1 neurons

**Authors: *J. KELLY**[1], C. SHOONER[2], M. J. HAWKEN[1], J. A. MOVSHON[1];
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**Abstract:** In primary visual cortex (V1), responses to stimuli at a neuron's preferred orientation can be suppressed by superimposing an orthogonal stimulus within the receptive field. This cross-orientation suppression can be at least partly explained by nonlinear contrast coding in the retinogeniculate pathways upstream of V1. However, the strength of this contextual masking (normalization) effect varies widely from neuron to neuron. We explored the sources of this variation by asking how other neuronal response properties and laminar location in cortex relate

to contrast normalization. We made extracellular recordings from V1 in 9 macaque monkeys, using single microelectrodes or Neuropixels arrays. We measured responses to gratings at multiple contrasts at the preferred orientation, with and without a superimposed 50% contrast orthogonal grating. Most cells were assigned to cortical layers based on postmortem histology. Cross-orientation masking effects can be described by a ratio of the response to high contrast plaids and a linear prediction made by summing the responses to the component gratings. Across the population, this measure revealed response patterns ranging from strong suppression to facilitation by the orthogonal mask. Facilitation was almost exclusively observed in complex cells recorded in the supragranular layers. Normalization can be more sensitively quantified by a mask-induced rightward shift in the contrast response function (a change in contrast gain). V1 neurons also differed widely by this measure, and a substantial number of V1 neurons showed little or no normalization. Normalization was strongly related to contrast sensitivity, with more sensitive neurons showing a stronger effect. We used a cluster analysis to learn how variations in normalization strength were associated with other neuronal response properties. Each of the principal clusters showed a unique distribution of sensitivity and response dynamics and was biased toward a particular subset of cortical layers. Two clusters contained many neurons with low thresholds and strong masking effects; these clusters had short response latencies and were concentrated in layer 4C. A long-latency supragranular complex cell cluster showed particularly low contrast sensitivity and minimal contrast gain effects. Our results suggest that subcortical nonlinearities in contrast coding explain a balanced relationship across the V1 population between contrast sensitivity and modulation by local contrast, but that the variation across clusters of cortical cells is largely determined by intracortical processing.

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**Poster**

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**Topic:** D.06. Vision

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**Title:** Narrow-band gamma oscillations in mouse V1 track local luminance in natural stimuli

**Authors: L. MEYEROLBERSLEBEN**[1,3], A. SIROTA[2,4], *L. BUSSE[1,4];
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Germany; [3]LMU Munich, Grad. Sch. of Systemic Neurosciences (GSN), Munich, Germany; [4]Bernstein Ctr. for Computat. Neurosci., Munich, Germany

**Abstract:** Throughout the brain, fine time scale coordination of neural activity is associated with the presence of fast oscillations, which have been hypothesized to serve a range of functions, including synchronization, communication, and information processing. Extensive research has focused on these brain rhythms in the mammalian visual thalamocortical system, where recent studies in mice have identified a prominent narrowband (NB)-gamma rhythm (centered at 50 - 70 Hz, with a narrow bandwidth of 5 - 7 Hz; Saleem et al., 2017). NB-gamma is elicited by full-field visual stimuli with uniform, high luminance, but it is suppressed by stimuli with high contrast. This stimulus selectivity of NB-gamma raises questions about its functional relevance in visual information processing. Specifically, the role of NB-gamma remains unclear under natural conditions, where visual input involves complex spatio-temporal distributions of luminance and contrast. Here, we show that NB-gamma tracks local luminance in natural scenes and recruits V1spiking with retinotopic specificity. Using extracellular recordings in head-fixed mice and data from the Allen Neuropixels Visual Coding project, we show a tight correlation between the NB-gamma power in the V1 local field potential (LFP) and local luminance in static natural scenes, specifically in the region of the scene covered by the receptive fields of the recorded population. Such tracking of local luminance was unique to NB-gamma, as the power of neighboring frequency bands was instead correlated with the images' local spatial-frequency power. Importantly, high local luminance not only predicted NB-gamma power in the V1 LFP, but also recruited spiking activity of individual V1 neurons with retinotopic specificity. Furthermore, we observed a similar representation of local luminance by NB-gamma for natural movies, where bursts of NB-gamma oscillations in the V1-LFP were preceded by local increases in luminance. These findings suggest that NB-gamma can serve as a temporal organizer of local V1spiking activity in conditions of high local luminance in naturalistic stimuli. Through contributions to the encoding of local luminance information, NB gamma might thus have a potential functional relevance for natural vision.

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**Topic:** D.06. Vision

**Support:** NRF-2023R1A2C2007289

**Title:** Behavioral evidence of predictive coding: Contrast sensitivity enhanced for stimuli matching the prediction from the preceding information

**Authors: *S. SONG**[1], M. PARK[2], C.-Y. KIM[1];
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**Abstract:** Predictive coding model has provided the viewpoint of studying the human brain as the organ of inference (Friston, 2018), with evidence from many findings that the top-down effect of predictive information can be reflected even in the earliest sensory neural activities (Rao & Ballard, 1999). However, it remains as a question whether those predictive effects can indeed lead to enhancement in low-level perceptual performance. Therefore, this study aimed to examine the impact of predictive information on contrast sensitivity, one of the fundamental human visual abilities. Gabor patches were selected as the visual stimuli to test contrast sensitivity and to generate prediction. The experimental task was a 2-alternative-forced choice task of reporting the tilted orientation of the target Gabor patch with keyboard press (i.e., left or right). Importantly, preceding the target, a stream of three Gabor patches were presented according to the three conditions; two prediction conditions, matching and nonmatching, and a control condition without prediction. For the prediction conditions, three Gabor patches whose orientations differed in regular steps of 30° were presented sequentially as preceding information, thus inducing the impression of rotation. In the matching condition, the target Gabor patch was presented in the angle matching the direction of stream rotation while the nonmatching target was in the orthogonal angle. The angles of preceding stimuli in the control condition were selected randomly and irregularly to prevent the generation of any predictive information. The contrast sensitivity of 50% threshold was measured by the adaptive 1-up-1-down staircase procedure. Threshold for each condition was measured by individual staircases. The result showed enhanced contrast sensitivity in the matching condition, compared to the nonmatching or the control conditions. Importantly, contrast sensitivity in the nonmatching condition was not lower than in the control condition—the participants made a response based on their perceptual experience, rather than passively reporting in a biased way following the preceding information. The current finding suggests that preceding predictive information can lead to enhancement in contrast sensitivity to the following target. This supports the idea that the predictive processing paradigm can also be extended to low-level visual perception, providing evidence for the link between the previous neural findings and behavior.

**Disclosures: S. Song:** None. **M. Park:** None. **C. Kim:** None.

**Poster**

**PSTR028. Processing of Contrast, Form, and Color**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR028.14/AA3

**Topic:** D.06. Vision

**Support:** NIH Grant EY027361

**Title:** Contrast sensitivity of ON and OFF human retinal pathways in myopia

**Authors: *S. POUDEL**, J. JIN, H. RAHIMI-NASRABADI, S. DELLOSTRITTO, M. W. DUL, S. VISWANATHAN, J.-M. ALONSO;
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**Abstract:** The visual system processes light and dark stimuli with ON and OFF visual pathways that respond differently to contrast. ON pathways have higher contrast sensitivity than OFF pathways in the retina, thalamus, and visual cortex of several species and, in human visual cortex, the ON-OFF sensitivity differences increase with luminance range (defined as the maximum minus luminance in the scene). Here, we demonstrate that, in human retina, the ON-OFF sensitivity differences also increase with luminance range and are affected by myopia, a visual disorder that elongates the eye and blurs vision at far distances. Human retinal responses were recorded with electroretinography using Dawson-Trick-Litzkow electrodes (13 females, 13 males; 29.9 ± 8.9 years old; eye axial lengths: 21.82 to 29.53 mm). ON and OFF retinal responses were driven with the onset of light and dark flashes presented on a bright background of 500 cd/m$^2$ in a Ganzfeld globe (ColorDome; Espion system). Contrast response functions were measured at two different luminance ranges, 500 and 250 cd/m$^2$, and fit with Naka-Rushton functions to extract three function parameters: the voltage response at 100% contrast ($R_{100}$), the luminance contrast generating half-maximum response normalized by the luminance range (C50n), and the response latency. Our results demonstrate that ON retinal pathways have higher contrast sensitivity (lower C50n) than OFF retinal pathways at both luminance ranges (ON/OFF C50n for 500 and 250 cd/m$^2$ range: 0.40 ± 0.09/0.61 ± 0.07, p = 2x10$^{-9}$ and 0.55 ± 0.13/0.71 ± 0.15, p = 0.011, Wilcoxon tests). They also demonstrate that increasing retinal illuminance makes contrast sensitivity higher in ON than OFF retinal pathways and responses stronger in OFF than ON retinal pathways. As a consequence, retinal illuminance is significantly correlated with both the OFF/ON ratio of contrast sensitivity and the OFF/ON ratio of response strength (OFF/ON C50n: r = 0.64, p = 0.0009; OFF/ON $R_{100}$: r = 0.81, p = 1 x 10$^{-6}$). Our results also demonstrate that myopia makes ON pathway responses weaker, less sensitive to contrast, slower, and less effective and slower at driving pupil constriction (pupil constriction is driven by ON pathways in mammals). As a consequence, eye axial length is significantly correlated with ON pathway response strength, latency, and mean pupil size ($R_{100}$: r = -0.51, p = 0.007; latency: r = 0.51, p = 0.007; mean pupil size: r = 0.41, p = 0.009). Based on these results, we conclude that contrast sensitivity is higher in ON than OFF retinal pathways but is compromised in myopia, a visual disorder that makes ON pathways weaker, slower, and less effective at protecting the retina from bright light.

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**Poster**

**PSTR028. Processing of Contrast, Form, and Color**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR028.15/Web Only

**Topic:**

**Title:** A meta-analysis of the neurological condition for visual agnosia and its opposite case

**Authors: *C. WU**;
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**Abstract:** Prof. Semir Zeki is a prominent investigator of the functional architecture of the primate (including Homo Sapiens) visual brain and has contributed substantially to our knowledge concerning the neural basis of color vision. His claim (in his "A century of cerebral achromatopsia", p.1765) that cortical achromatopsia on the one hand, and visual agnosia with intact color vision on the other, constitute two opposite neurological conditions, however, is not neuroanatomically well substantiated. As early in 1892, the Swedish neurologist Salomon Eberhard Henschen already classified hemianopia (in which the visual consciousness for the affected visual field is lost) and agnosia (i.e., "Seelenblindkeit" as this condition was referred to at his time) are a pair of opposite neurological classes: The former is with lesion in the primary visual cortex (V1, or "calcarine cortex" as referred to at his time) and with largely intact extra-striatal cortical areas, whereas the latter is just the opposite - that is, with intact V1 and damaged extra-striatal cortex. Moreover, he used these two neurological conditions as positive and negative cases to establish V1 as the "vision center" in the human brain (in his "Klinische und anatomische Beiträge zur Pathologie des Gehirns", vol.2, p.280) . Here I present a meta-analysis of the relevant neurological cases described by Henschen himself and several more visual disorder cases reported after Henschen in the neurological literature. Some of these cases have clear neuroanatomical information regarding the patients' brain lesions, available through either autopsy neuroanatomical analysis (including some of the brains studied by Henschen, with brain damage patterns carefully drawn and presented as Karte G & H in his work cited above) or PET scanning / fMRI imaging in living patients. Overall, this analysis indicates that (1) Henschen's characterization of hemianopia vs. agnosia as two opposite neurological conditions is more appropriate than Zeki's view concerning cortical achromatopsia vs. agnosia, in terms of the brain damage patterns associated with these neurological conditions; (2) V1 is in fact what Henschen states as the "vision center" in the sense that it is a neural substrate for a primary type of visual consciousness - namely, the sensation for light and colors. Presently, Henschen's conclusion about V1 has largely been forgotten; but here I attempt to reinstate this conclusion with an analysis of a set of relevant neurological cases as well as from an associationism's point of view which had precisely summarized by the prominent Scottish scientist James Clerk Maxwell as "all vision is color vision" (Nature, vol.4, p.13).

**Disclosures: C. Wu:** None.

**Poster**

**PSTR028. Processing of Contrast, Form, and Color**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR028.16/AA4

**Topic:** D.06. Vision

**Title:** Alpha Echoes in Low-Level Visual Feature Processing Originate in V1 and Propagate Up the Visual System

**Authors: *A. MORROW**, A. PILIPENKO, E. TURKOVICH, S. SANKARAN, J. SAMAHA;
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**Abstract:** Understanding how specific stimulus properties are maintained and distributed in the brain is critical to understanding how we are able to process and respond to varying perceptual phenomena in our everyday environment. Using cross-correlation between EEG signals and random luminance sequences, it was found that a luminance change leads to a long-lasting "echo" in the alpha frequency range (VanRullen & Macdonald, 2012). The neural origin of these echoes and the precise stimulus features that induce them have not been extensively studied. Here, we presented stimuli that vary randomly over time in their luminance values or contrast value and also manipulate the visual field location of the stimuli in order to examine the origin of the responses in early retinotopic areas. We found that the initial wave of the echo showed a clear polarity reversal based on upper or lower visual field location and then the phase difference quickly disappeared, suggesting that the echo begins in the primary visual cortex (V1) and then propagates up the visual system. We found a similar pattern for both luminance-based echoes and contrast-based echoes, although the contrast echoes were shorter-lived. Our results shed new light on stimulus properties that produce visual echoes as well as provide novel evidence that the echoes behave as traveling waves originating in V1.

**Disclosures: A. Morrow:** None. **A. Pilipenko:** None. **E. Turkovich:** None. **S. Sankaran:** None. **J. Samaha:** None.

**Poster**

**PSTR028. Processing of Contrast, Form, and Color**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR028.17/AA5

**Topic:** D.06. Vision

**Support:** TL1 TR003169

**Title:** A Deep Learning Approach to Naturalistic Surround Modulation

**Authors: *M. SLAPIK**, A. ANDREI, S. KHAN, V. DRAGOI;
McGovern Med. Sch., Houston, TX

**Abstract: Introduction:** Although each neuron in visual cortex is like a spotlight that responds to a specific region of the visual field, its response can also be modulated by stimuli surrounding that spotlight through horizontal connections. These contextual effects have generally been studied in the context of simple grating stimuli, but it is unclear how they operate in the context of naturalistic stimuli. Using new machine learning techniques, we design optimal surround stimuli that incorporate naturalistic features. In the process, we better capture the functioning of

visual cortex in everyday life.
**Methods:** We present visual stimuli to a macaque monkey on a computer monitor, and record from early visual cortex (V1) using a Plexon laminar electrode. Our machine learning algorithm was pioneered by Ponce et al. (2019) and consists of two components: an image generator and an optimizer. The image generator, a generative adversarial network or "GAN," is trained on over a million natural images and can flexibly produce a wide range of stimuli that resemble textures, objects, and landscapes. Meanwhile, our optimizer, a co-variate matrix adaptation evolution strategy or "CMA-ES," uses neural feedback to iteratively evolve these stimuli and maximize the firing rate of a target neuron in visual cortex.
**Results:** Our results validate a new method of studying surround modulation in visual cortex. By combining an image generator and an optimizer, we can consistently develop "optimal surround stimuli" that outperform traditional surrounds such as oriented gratings. These optimal surround stimuli tend to incorporate preferred orientations and colors as measured by single-modality tasks, showing how these features optimally combine in naturalistic images. However, they also include suboptimal orientations and colors, as well as more complex features like textures and shapes not traditionally associated with early visual cortex. These findings reveal the diverse tunings of early visual cortex in response to naturalistic stimuli.
**Discussion:** In this study, we demonstrate the power of using machine learning and neural feedback in stimulus design. Optimal surrounds stimuli outperform traditional, single-modality surrounds and incorporate a diverse range of visual features such as color, shape and texture. This supports an overarching view of visual cortex as encoding multi-faceted, naturalistic features rather than simple, single-modality features like orientation or color alone. Furthermore, it shows how neural feedback can be used to guide stimulus design and discover new properties of neural circuits.

**Disclosures:** **M. Slapik:** None. **A. Andrei:** None. **S. Khan:** None. **V. Dragoi:** None.

**Poster**

**PSTR029. Timing and Temporal Processing I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR029.01/AA6

**Topic:** H.10. Human Learning and Cognition

**Support:** R01 DA048096
R01 MH121099
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KL2TR00142

**Title:** Monetary reinforcement influences time perception and temporal learning for 1000ms-intervals, but not 3000ms- or 5000ms-intervals

**Authors: *E. K. DIMARCO**, A. R. SHIPP, K. T. KISHIDA;
Wake Forest Univ. Sch. of Med., Winston-Salem, NC

**Abstract:** Time perception is a fundamental cognitive process that is altered in many brain disorders. Interval timing, operationally defined as the perception of time ranging from millisecond to minute durations, is believed to be modulated by striatal dopamine and is often measured using instrumental learning tasks that present subjects with intervals of time then positively reinforce correct behavior. These task structures, as well as the evidence that interval timing is modulated by striatal dopamine, have led to the hypothesis that interval timing behavior can be explained using reinforcement learning theory. To investigate the intersection of reinforcement learning and interval timing mechanisms, we first sought to characterize the effects of reinforcement on interval timing behavior. We executed three studies (PIP-neutral, N=24, PIP-same-magnitude, N=24; and PIP-reinforcement, N=40), each implementing a variation on a three-interval timing task to measure participants ability to reproduce 1000ms, 3000ms, and 5000ms intervals of time in the presence and absence of reinforcers with different valence and magnitude. We found that interval timing behavior is altered based on reinforcement (presence or absence), valence (positive or negative) and magnitude (scaled to interval duration or fixed). Specifically, we found reinforced cues produce significantly higher rates of initial error but also higher rates of learning over repeated trials compared to non-reinforced cues for the 1000ms duration, but not the 3000ms or 5000ms durations (mixed effects ANOVA; $p < 0.05$). We observed that reinforced tasks elicit temporal behavior that generalizes across reinforcement valence (positive, negative, neutral; pairwise t-tests; $p < 0.05$). Additionally, we show that reward prediction errors (better or worse than expected rewards) on previous trials are correlated with performance prediction errors on subsequent trials (linear regression model; $p < 0.05$). The results of these experiments may serve as an initial step to integrating an understanding of reinforcement learning theory, interval timing, and potentially shared dopaminergic mechanisms.

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**Poster**

**PSTR029. Timing and Temporal Processing I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR029.02/AA7

**Topic:** H.10. Human Learning and Cognition

**Title:** Effects of Transcranial Random Noise Stimulation (tRNS) on Time Perception Deficits in ADHD

**Authors: *F. ASAD**, M. PETERSON, M. WIENER;
IPN, George Mason Univ., Fairfax, VA

**Abstract:** Effects of Transcranial random noise stimulation (tRNS) on TIME PERCEPTION DEFICITS IN ADHDFatima Asad[1], Matthew Peterson[12,3,4] & Martin Wiener[1,2], 1. Cognitive and Behavioral Neuroscience Program, 2.Interdisciplinary Program in Neuroscience, Human Factors and Applied Cognition Program, Center for AdvancingHuman-Machine Partnerships, Department of Psychology, George Mason University, Fairfax VA and Department

ofPsychology, George Mason University, Fairfax VA.ADHD is the most prevalent mental disorder affecting children, characterized by inattention, impulsivity, andhyperactivity. It is widely recognized as a lifelong condition which can significantly impact various areas of anindividual's life, such as academic and career pursuits, social relations, and daily activities etc. As of 2016, it wasestimated that approximately 6.1 million children in the United States aged 2-17 years old (which amounts to 9.4% ofthis age group) had received a diagnosis of ADHD. Although not used as a diagnostic symptom, time perception is acommon deficit found in ADHD individuals, with individuals with ADHD tending to overestimate time compared tonormally developing controls. When asked to reproduce time in a task, individuals with ADHD tend to produce longerintervals compared to controls. Previous work has suggested that the source of ADHD deficits in timing comes fromprefrontal cortical sites, characterized by over-activation in this region. We hypothesized that applying transcranialrandom noise stimulation (tRNS) over prefrontal regions in ADHD may improve timing performance. Two groupsof individuals, age 18-40, with and without a diagnosis of ADHD (n=20 ea.) were tested on a time reproduction task(0.6-1s) while receiving either sham or active stimulation to the F2 region of the brain. The results demonstrated thattRNS to control subjects lengthened time estimates, consistent with previous results. However, tRNS had no effecton individuals with ADHD. These findings support differential prefrontal mechanisms in ADHD that modulate theeffects of brain stimulation and suggest that underlying differences in attention may relate to heterogeneity in brainstimulation effects.

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**Poster**

**PSTR029. Timing and Temporal Processing I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR029.03/AA8

**Topic:** H.10. Human Learning and Cognition

**Support:** Department of Defense W81XWH1910685
Edward and Barbara Bell Family Chair

**Title:** Utilizing augmented reality to evaluate service member team performance

**Authors: *R. KAYA**[1], K. HASTILOW[1], K. M. OWEN[1], E. M. ZIMMERMAN[1], A. ROSENFELDT[3], J. L. ALBERTS[2];
[2]Cleveland Clin., [1]Cleveland Clin., Cleveland, OH; [3]Cleveland Clin. Fndn., Cleveland, OH

**Abstract: Introduction:** Decision making is a complex process that relies on situational awareness and experience to create a potential list of actions while weighing the benefits and pitfalls of each action. Evaluating decision making amongst team members in a real-life environment where perception and action are coupled is critical to understanding decision-making in service members. There is a dearth of data evaluating decision-making for service

members during the performance of ecological tasks. **Purpose:** To create military specific room breaching and clearing scenarios in augmented reality with distinct room environments to assess decision making capabilities in service members. **Methods:** One-hundred ten military service members from Fort Benning Georgia participated in this project. Service members completed three room breaching and clearing scenarios (empty room, a hostile environment with a civilian (Go-No-Go) and an incorrect positioning of a unit member) in an augmented reality environment with three digital avatar unit members. Three dimensional position data from the Microsoft HoloLens 2 headset was captured and used to compute temporal measures of room breaching and clearing events. Temporal outcomes included time to enter room, time to fire first shot, time in fatal funnel, and total trial time. **Results:** Linear mixed effects revealed between scenario differences for all scenarios ($p < 0.0001$). Pairwise comparisons between the incorrect position scenario and the Go-No-Go condition demonstrated no difference in time to enter the room (2.36 s in both scenarios); however, time to fire the first shot in the Go-No-Go scenario was longer (0.97 s to 0.58 s) while time in fatal funnel (2.58 s to 3.31 s) and time to trial completion (7.46 s to 8.41 s) was longer in the incorrect position scenario. **Conclusions:** These data reflect a change in decision making capabilities during a military specific, ecological, team based scenarios when altering the environment inside of the room. Future studies are planned to evaluate the effects of mild traumatic brain injury on service member team performance.

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**Poster**

**PSTR029. Timing and Temporal Processing I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR029.04/AA9

**Topic:** H.10. Human Learning and Cognition

**Title:** Examining multiscale entropy in cannabis users: insights into brain complexity

**Authors: *W. T. CREEL**, R. HARTMAN, C. BRENNER;
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**Abstract: Background.** The use of cannabis has become increasingly prevalent, raising questions about its potential impact on neural dynamics and cognitive processing. Although research has shown that cannabis dependence is associated with increased brain complexity using a single-scale index (Laprevote et al., 2017), it is currently unknown how cannabis use effects underlying neural dynamics across temporal scales. Multiscale entropy (MSE) analysis provides nuanced insight into underlying brain dynamics by examining changes in signal complexity across fine and coarse temporal scales, reflecting local and global information processing, respectively. **Method.** The current study analyzed resting-stage EEG data from 61 participants (62.3 % female) grouped by frequency of use (frequent users, low-frequency users, and non-users) to determine whether group differences exist in signal complexity across

temporal scales. MSE was implemented using the EntropyHub toolkit for Python. MSE values were calculated on independent channels before averaging across all channels for each participant. Subsequently, MSE values were averaged across subjects to obtain MSE curve profiles for all three groups. Between-group differences in MSE values were obtained using a one-way MANOVA. **Results.** Preliminary data suggest that frequent cannabis users exhibit decreased complexity at both fine and coarse scales compared to non-users and low-frequency users with markedly decreased complexity levels in frontal lobe channels. **Conclusions.** Initial findings suggest that frequent cannabis users exhibit less complex brain activity, potentially reflecting less efficient and flexible information processing both locally and globally, with most noticeable alterations in the frontal lobe region. These contrasting results with prior research highlight the importance of accounting for the multiple time scales inherent in physiological systems to capture the full range and complexity of underlying neural dynamics.

**Disclosures: W.T. Creel:** None. **R. Hartman:** None. **C. Brenner:** None.

**Poster**

**PSTR029. Timing and Temporal Processing I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR029.05/AA10

**Topic:** H.10. Human Learning and Cognition

**Support:** NSERC RGPIN-2023-05054
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CRC-2019-00107
CFI/ORF-2014-34479
OGS

**Title:** Determining individualized neural event boundaries using fMRI

**Authors: *R. E. WILFORD**, E. WHARTON-SHUKSTER, H. CHEN, A. S. FINN, K. D. DUNCAN;
Dept. of Psychology, Univ. of Toronto, Toronto, ON, Canada

**Abstract:** Our ongoing experience is segmented into a nested series of discrete events, behaviourally and neurally separated by boundaries (Zacks et al., 2007). This segmentation is so strongly associated with shifts in brain activity patterns, that researchers can decode event transitions in movies and auditory narratives using fMRI (e.g., Baldassano et al., 2017). Current neural state segmentation techniques manage the inherent noisiness of fMRI data by identifying state transitions within group-averaged data, with the logic that neural state transitions that are related to event boundaries are shared whereas noise is idiosyncratic (Baldassano et al., 2017; Geerligs et al., 2021). While this is a reasonable starting point, the consistent variability in behavioural event boundary agreement (e.g., Zack & Tversky, 2001; Baldassano et al., 2017) suggests that the perception of event boundaries is itself idiosyncratic, such that averaging across

people too early in the pipeline could miss much of the tool's potential to capture this information. As such, we aim to assess whether the Greedy State Boundary Search (GSBS) algorithm (Geerligs et al., 2021) can reliably identify individualized neural boundaries. As a first step, we applied GSBS to individual participant data in a publicly available fMRI dataset where 67 children ages 5-21 watched a clip of the movie Despicable Me (Alexander et al., 2017). We have promising preliminary results in the posterior parietal cortex, a region known to correspond well with normative judgments at the group-level (Baldassano et al., 2017). When we subsequently averaged these individualized boundaries across participants, the timeseries correlated well with normed behavioural boundary timing ($p<.0001$). Further, both the number of neural boundaries ($p<.0001$) and the correspondence of inter-subject boundary timing ($p<.0001$) increased with age, mirroring developmental patterns found in boundary judgements (Benear et al., 2023; Ren et al., 2021; Yates et al., 2022). And while motion estimates negatively correlated with the number of boundaries, they do not explain these developmental trends. Together, these results suggest that GSBS could be used to identify meaningful individualized neural boundaries. Finally, we will explore the effects of different denoising and aggregation procedures on our ability to reliably detect individualized boundaries, ending with recommendations for best practices. These promising preliminary results highlight the importance of developing and validating fMRI tools for the individual level of analysis; what meaningful insights could we be missing when we average away what makes each of us unique?

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**Poster**

**PSTR029. Timing and Temporal Processing I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR029.06/AA11

**Topic:** H.10. Human Learning and Cognition

**Title:** Towards a Generalizable Model to Detect Cognitive Loading Events with Eye-Tracking

**Authors: *Q. DANG**[1], M. ANORUO[2], M. KUCUKOSMANOGLU[2], S. CONKLIN[2], G. KARGOSHA[2], J. BROOKS[2];
[2]Computer Sci. and Electrical Engin., [1]UMBC, Baltimore, MD

**Abstract:** Pupil size has been used as an indicator of cognitive load since diameter increases with task difficulty and reflects changes in attention and arousal mediated by the autonomic nervous system. This study investigated the potential of detecting the precise onset of cognitively loading events by analyzing pupil and eye movement responses across a variety of laboratory-based tasks for which stimulus onset was known. Participants (n=58) completed the Dot Probe Task (DPT), Mental Arithmetic (MA), Psychomotor Vigilance Task (PVT), and Visual Working Memory (VWM) while eye-tracking parameters (i.e. pupillometry and gaze position) were recorded. The problem was framed as a binary classification task, labeling 1-second windows as

"1" if they occurred immediately after a trial onset, and "0" otherwise. A Convolutional Neural Network (CNN) architecture was employed as the model for training the tasks, and the model's performance was evaluated using the F1 score metric. Among the tasks, the DPT demonstrated the highest F1 score of 0.91, followed by MA (0.82), PVT (0.80), and VWM (0.39). When training all four tasks together, the model achieved an F1 score of 0.72, indicating limited generalization ability. Although the general model underperformed compared to the individual DPT, MA, and PVT tasks, it displayed promising results beyond random guessing. The average F1 score using both pupil size and gaze position was 0.72, only slightly dropping to 0.67 when gaze position was excluded. The CNN model effectively detected common patterns in pupil size, where the pupil initially constricted after the onset and followed by a pupil dilation related to cognitive workload. Our preliminary findings suggest that after the onset, the constriction in pupil size indicated participants' attentional shift toward the newly presented problem, with pupillary light reflexes only making a minor contribution to the constriction. The shifting focus took about 0.6 to 0.8 seconds. Subsequently, the pupil dilation indicated the onset of cognitive workload, with the peak of pupil size and the latency of the peaks strongly influenced by the cognitive workload magnitude and task duration. For short tasks such as PVT, peaks occurred around 0.5 to 1 second after the onset, while medium tasks like VWM and DPT exhibited peaks around 1.5 to 2.5 seconds. Longer tasks like MA typically showed peaks after approximately 3.5 seconds. These findings emphasize the potential of machine learning to accurately predict cognitive load based on pupil and eye movement responses, contributing to advancements in personalized learning and optimizing neurocognitive workload allocation.

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**Poster**

**PSTR029. Timing and Temporal Processing I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR029.07/AA12

**Topic:** H.10. Human Learning and Cognition

**Support:** Samsung Research Funding & Incubation Center for Future Technology (SRFC-IT1902- 08, Decoding Inner Music Using Electrocorticography)
Basic Science Research Program through the National Research Foundation of Korea (NRF-2021R1A4A200180312)
Basic Science Research Program through the National Research Foundation of Korea (NRF-2022R1I1A1A0107380012)

**Title:** Perceptual reversal between voices in music reflected by connectivity from the left inferor frontal gyrus to the right Heschl’s gyrus

**Authors: *C. KIM**[1,2,3], C. CHUNG[4,5,2,3];
[1]Dent. Res. Inst., Seoul, Korea, Republic of; [2]MEG Center, Dept. of Neurosurgery, Seoul Natl.

Univ. Hosp., Seoul, Korea, Republic of; [3]Interdisciplinary Program in Neuroscience, Seoul Natl. Univ. Col. of Natural Sci., Seoul, Korea, Republic of; [4]Dept. of Brain and Cognitive Science, Seoul Natl. Univ. Col. of Natural Sci., Seoul, Korea, Republic of; [5]Dept. of Neurosurgery, Seoul Natl. Univ. Hosp., Seoul, Korea, Republic of

**Abstract:** How we can hear one voice while another voice is not heard, and the how the situation reverses naturally during music listening are still not well understood. Here, we examined the modulations of frontotemporal connectivity from the left inferior frontal gyrus (IFG) to the right Heschl's gyrus (HG) in response to the Twinkle Twinkle Little Star (TTLS) melody, as participants listened to Mozart's Variations KV 265. Our findings reveal that frontotemporal connectivity, specifically from the left IFG to the right HG, undergoes dynamic changes at the conclusion of repeated musical phrases. Interestingly, these connectivity changes coincide with the perceptual reversal of the TTLS melody, where it transitions from being perceived as the prominent figure during the initial phase to the lower voice being processed as the figure in later repeated phrases. The observed figure-ground reversal in repeated passages was strongly reflected in the modulation of frontotemporal connectivity. This study provides compelling evidence for how the human brain dissects voices from the multidimensional structures of continuously changing music and reconstructs them through momentary switches in figure-ground processes. The implications of these findings shed light on the neural mechanisms underlying voice perception in complex musical environments.

**Disclosures: C. Kim:** None. **C. Chung:** None.

**Poster**

**PSTR029. Timing and Temporal Processing I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR029.08/AA13

**Topic:** H.10. Human Learning and Cognition

**Support:** Source of funding: Intramural Research Program at the National Eye Institute (NEI)

**Title:** Long-term color-shape learning in macaque monkeys

**Authors: *A. C. R. GREEN**[1], J. CAVANAUGH[1], S. R. LOGGIA[1], S. SINGH[1], S. AWASTHI[1], H. E. FEIBES[1], B. B. AVERBECK[2], B. R. CONWAY[1];
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**Abstract:** Humans use shape and color to identify and select objects. Prior work has raised three questions about this behavior: Are learning rates different for shapes and colors? Does knowledge of color-shape associations impact color perception? Why are the colors of “objects” more likely to be warm than cool? We tested macaques, a model of humans, to address these questions. We collected data over four years in two juvenile macaques using in-cage touch

screens. All experiments involved 12 “objects” (2-D colored shapes) in which color and shape were equally diagnostic of identity. Colors were six equally saturated hues of both luminance polarity that evenly sample hue angle in CIELUV color space. Phase I tested and trained selection of an object’s color or shape. Trials began by presenting an object. In some trials monkeys were rewarded for choosing from four options the blob of matching color; in other trials, they were rewarded for picking the matching colorless shape. Phase II tested the learned color-shape associations. Trials began with a colored blob or colorless shape of one of the 12 objects, and monkeys were rewarded for selecting the associated shape or color. Using a reinforcement-learning framework, we estimated initial performance, learning rate, and plateau performance. Monkeys learned to match objects to shapes faster than to colors (Phase I, likelihood ratio test, $p<0.01$), and learned to match shape cues to color faster than color cues to shape (Phase II, $p<0.01$), akin to human toddlers. Monkeys began near chance on Phase II, showing little evidence of cognitive penetration of color-shape knowledge. At plateau performance (Phase II, 96.8% accuracy), we began Phase III to assess how shapes and colors, when equally diagnostic, are used to identify objects. Trials began with one object followed by two options: 80% of trials, one option was a direct match; 20% of trials, both options matched either the object’s shape or color. Humans (n=96) completed an analogous task online. Humans and monkeys: (1) matched objects to shape more often than to color (t-test, $p<10^{-4}$); (2) were more likely to use color for objects of positive luminance-contrast polarity (ANOVA, $p=10^{-4}$); (3) were less likely to choose color for yellow or purple objects. Interestingly, humans were more likely than monkeys to match objects to color for warm-colored than for cool-colored objects (ANOVA, human: $p=0.006$; monkey: $p=0.72$), suggesting that the diagnostic use of color by humans reflects a prior about colors of behaviorally relevant things, not an innate preference for warm colors.

**Disclosures:** **A.C.R. Green:** None. **J. Cavanaugh:** None. **S.R. Loggia:** None. **S. Singh:** None. **S. Awasthi:** None. **H.E. Feibes:** None. **B.B. Averbeck:** None. **B.R. Conway:** None.

**Poster**

**PSTR029. Timing and Temporal Processing I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR029.09/AA14

**Topic:** H.10. Human Learning and Cognition

**Support:** NIH Grant R01 MH100121
NSF GRF 2023350133

**Title:** Specific temporal memory and general temporal knowledge interact during development

**Authors: O. FRIEND**;
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**Abstract:** Our conception of time is essential to episodic memory, providing a frame of reference with which we can (1) distinguish specific events from one another and (2) generalize knowledge across them. For example, memory of a specific morning may allow you to recall that you ate breakfast at 8 AM (*specific temporal memory*) while integration of temporal information across different mornings (e.g., breakfast at 8 AM and 9 AM) may enable abstraction of the knowledge that breakfast typically occurs at 8:30 AM (*general temporal knowledge*). These specific and general facets of temporal memory are thought to alternately rely on within-event and between-event memory processes, which may develop at different ages. Past developmental work indicates that children can recall precise temporal details of single events (Reese et al., 2011), but less is known about whether they generalize temporal information across events. Given that the ability to integrate across events shows protracted development (Bauer, 2021), one proposition is that children may be less likely to form general temporal knowledge. Here, we test this idea, assessing whether there is a bias toward specific temporal memory earlier in life before general temporal knowledge emerges. To that end, individuals 7-28 years completed a child-friendly adaptation of an adult temporal memory task (Bellmund et al., 2022) in which they learned a sequence of five events and were asked to remember the precise time of each (*Specific Time*; Event 1 - 8 AM, Event 2 - 11:30 AM). Critically, participants were exposed to four separate sequences, each adhering to the same 5-event structure, such that generalization across events in the same temporal position was also possible (*General Time;* Average time of Event 2 across sequences). Preliminary results (n=61) show non-linear development of memory for specific time, with the largest improvement in childhood (7-10 years) and linear increases into adulthood. In addition, we show that specific temporal memory was biased toward average times at all ages, suggesting that even children extracted general temporal knowledge. Importantly, general temporal knowledge tracked with specific temporal memory, particularly among children, such that greater generalization tracked lower specificity. Together, the findings suggest that temporal generalization interacts with children's ability to reconstruct specific event times, with this imprecise temporal framing leading to specificity errors. We speculate that, in contrast to adults who effectively form both specific and general temporal memories, children may rely on general temporal memory to compensate for underdeveloped specific memory.

**Disclosures: O. Friend:** None.

**Poster**

**PSTR029. Timing and Temporal Processing I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR029.10/AA15

**Topic:** H.10. Human Learning and Cognition

**Support:** WPI grant
Kakenhi grant 23KJ0586

**Title:** Lateralization of neural sources during hierarchical temporal predictions

**Authors: *Y. T. HUANG**, S. KOIKE, Z. C. CHAO;
Univ. of Tokyo, Tokyo, Japan

**Abstract:** Have you noticed that your anticipation of a green light is increasing as waiting longer at a crossroad? This dynamic prediction of *when* an event will take place can be described by the hazard function, a conditional probability of an event (the green light) to occur at a specific time, given that it has not occurred yet. However, temporal prediction in real life could be established by learning hierarchical statistical regularities such as predicting the timing of the next beat based on priors of single beat and multi-beat sequence in music, and it remains unclear how the brain represents the hierarchical temporal prediction. Here, foreperiod (FP) is the time interval between warning and target stimuli, and the participant needed to quickly respond to the target by considering two levels of probability distributions of the FP. For example, the FP could be 50% short and 50% long (first level: single FP), but could be 100% short when the precedent FP was short (second level: two-FP sequence). Therefore, the temporal prediction can be described by two hard functions, HF1 and HF2, respectively based on the first- and second-level probability distributions. Behaviorally, a linear mixed-effect model incorporating both HF1 and HF2, compared to only HF1 and only HF2, was the most effective predictor of reaction time. This suggested that two-level regularities were collectively employed to formulate temporal predictions. Moreover, we adopted a forward encoding model to capture correlations between two hazard functions and dynamics of EEG diploe sources. We found significant correlations in the hippocampus, premotor area, and cerebellum. Interestingly, HF1 was dominantly represented in the left cerebellum while HF2 was dominantly represented in the right cerebellum. Our findings revealed that multi-scale statistics for making temporal predictions were jointly encoded in distributed and hierarchy-specific lateralized brain networks.

**Disclosures: Y.T. Huang:** None. **S. Koike:** None. **Z.C. Chao:** None.

**Poster**

**PSTR029. Timing and Temporal Processing I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR029.11/AA16

**Topic:** H.10. Human Learning and Cognition

**Support:** T32 MH106454
National Science Foundation, Award # 1844792
RO1 MH060941

**Title:** Emotional Influence on Mnemonic Judgements of Temporal Proximity

**Authors: *A. NADIADWALA**[1], A. R. PRESTON[2,3], J. E. DUNSMOOR[4];
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**Abstract:** Prior memory research reveals how shifts in contextual states organize the content of episodic memory. For example, separate events experienced across a shift in context (i.e., event boundary) are judged as being experienced farther apart in time than equally separated events experienced within the same context. However, while emotion has a well-known impact on episodic memory, whether emotional states affect temporal organization of memory remains underexplored. For example, is information encoded in an emotional state perceived as occurring closer or farther in time than a neutral context? In this project, we investigated whether the emotional nature of contextual states affects temporal distance judgements for neutral information encoded within or across neutral and emotional contexts. Twenty-eight participants encoded pictures of neutral everyday objects, paired with a picture of a neutral scene image that was repeated across six consecutive trials. Critically, scene contexts were either associated with threat, defined as the possibility of receiving an unpredictable mild electrical shock to the wrist, or safety, defined as the absence of a possible shock. Threat and safety were explicitly indicated to the participant by the corresponding word presented below the scene context image. Physiological arousal was confirmed through measures of skin conductance level in the threat versus safety contexts. Immediately after encoding, participants viewed two neutral objects that had been presented either within or across contexts that were always separated in time by three intervening trials. Participants judged how close or far apart in time the two objects were presented during encoding. Results confirmed an effect of event boundaries on temporal judgements, such that objects presented across a context shift were judged as being farther apart than equally spaced objects presented in the same context. Interestingly, however, the emotional nature of the context did not affect temporal judgements either within or across event boundaries. Altogether, these findings suggest that emotional arousal did not determine temporal order judgements, perhaps indicating dissociation between the effects of emotion on separate aspects of mnemonic organization. Further research is needed to probe other aspects by which emotion impacts long-term episodic memory organization.

**Disclosures: A. Nadiadwala:** None. **A.R. Preston:** None. **J.E. Dunsmoor:** None.

**Poster**

**PSTR029. Timing and Temporal Processing I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR029.12/Web Only

**Topic:** H.10. Human Learning and Cognition

**Support:** TUBITAK 120K904

**Title:** Pupil dilation in time perception

**Authors: *C. INAN**[1], A. FAROOQUI[2], T. GEZICI[2];
[1]Psychology, [2]Neurosci., Bilkent Univ., Ankara, Turkey

**Abstract: Ausaf F. & Cansel I.**Time perception is our subjective view of the time passage and relates to the duration of comprehension, order, and pace of events in our environment. This complex process includes the integration of information from numerous sensory inputs along with higher-order cognitive functions including attention, recollection, and decision-making. It is well known that demands on attention, working memory, decision making, difficult perception, memory recall cause greater pupil size. Hence, during any type of effortful work, pupil size increases. We suggest that there are two different types of task demands in a prior study. Load (1) that is connected to what is being done right now, such enhanced working memory or attention. This type of load, which we refer to as load 1, is widely known. Yet, we propose a distinct and unidentified type of cognitive load (load 2). The duration of the present task episode has an impact on this load. This load results in us completing lengthy actions as a single unit, such as writing emails and shopping, rather than carrying out each of their numerous component acts separately. Longer tasks need the organization and regulation of thought and behavior over a longer time. We previously demonstrated that load 1 increased pupil size whereas load 2 lowered it. We put these predictions to the test in the present study using a duration replication task in which 30 subjects were recruited (22 women, aged 18–27). Subjects were presented with a cue screen with a target time duration (such as 11 seconds). On the next screen, subjects were asked to pay attention to the passage of time and perform a keypress when they think they reached the target duration. After the key press, subjects were presented with how much they deviated from the target interval. They were asked to replicate short (8–12 seconds) and long (14–18 seconds) intervals (two conditions). This was demonstrated by higher deviations during the longer intervals. The longer intervals, however, involved paying attention to the passing of time for a longer amount of time, which equated to a longer work episode, thus this requirement was associated with load 2. If as is often believed, any type of load increases pupil size, the effect should be greater when subjects reproduced a task for a longer period. Pupil size would be lower when subjects reproduced longer periods, yet, if pupil size declined as task length increased (i.e. load 2). We discovered that along the replication of longer intervals, pupil diameters were in fact lower, both early on and later on. We demonstrate that a particular type of cognitive load, contrary to the more well-known type of load, does not raise, but rather decreases pupil size.

**Disclosures: C. Inan:** None. **A. Farooqui:** None. **T. Gezici:** None.

**Poster**

**PSTR029. Timing and Temporal Processing I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR029.13/AA17

**Topic:** H.10. Human Learning and Cognition

**Support:** JSPS Kakenhi 22H00502
JSPS Kakenhi 22K18263

**Title:** Testing the correlations between the individuals' autistic traits and aftereffect in tactile synchrony judgment

**Authors: *K. WIDJAJA**[1,3], M. WADA[3], M. HAKAMATA[2], M. MIYAZAKI[1,2];
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[3]Developmental Disorders Section, Dept. of Rehabil. for Brain Functions, Res. Inst. of Natl. Rehabil. Ctr. for Persons with Disabilities, Saitama, Japan

**Abstract:** Individuals with autism spectrum disorder (ASD) have atypical time perception. Recent investigations demonstrated that individuals with high autistic traits are reported to not adapt to prior stimuli effectively. Previously, we found a positive aftereffect of prior asynchrony in tactile synchrony judgment (SJ) (Widjaja et al., 2019; 2022, Soc Neurosci Abst). Here, we further investigated the relationship between the autistic traits of the participants and the magnitude of the aftereffect in tactile SJ. Typically developed participants (n = 24) were engaged in an SJ task. In each trial, the participants either received an asynchronous [stimulus onset asynchrony (SOA): ± 100 ms] or a synchronous (SOA: 0 ms) adaptor stimulus pair. Then, 500 ms after the adaptor stimulus pair, the participants received a test stimulus pair (SOA: ± 80, ± 30, ± 10, or 0 ms) and judged whether the stimulus pair occurred synchronously or not. Each participant completed 378 trials of the task. The autistic traits of each participant were measured using the Japanese version of the Autism Quotient (AQ) (Wakabayashi et al., 2004, Jpn J Psychol). Consistent with our previous findings, we observed a positive aftereffect of prior asynchrony on SJ. That is, after the asynchrony adaptor was presented, the participants judged the test stimulus pairs as occurring asynchronously with greater frequency compared to that of the synchrony adaptor. Notably, the magnitude of the positive aftereffect exhibited a significant negative correlation with specific subscales of the AQ, namely the Attention to Detail and Communication traits. The more severe these autistic traits, the weaker the positive aftereffect is. Meanwhile, the correlation with the total AQ score did not reach a significant level. A previous study also reported weakened positive aftereffect in tactile temporal order judgment (TOJ) of individuals with higher autistic traits (Wada et al., 2023 J Autism Dev Disord). However, the significant negative correlation was observed between the magnitudes of the aftereffect and total AQ scores. SJ reflects the smaller psychological and neuronal components involved in human time processing (e.g., Miyazaki et al. 2016, Sci Rep). Accordingly, our results suggest that the magnitude of the positive aftereffect in tactile SJ reflects specific psychological and neuronal components associated with autistic traits, particularly the tendency to focus on fine aspects of information and the difficulty in communication.

**Disclosures: K. Widjaja:** None. **M. Wada:** None. **M. Hakamata:** None. **M. Miyazaki:** None.

**Poster**

**PSTR029. Timing and Temporal Processing I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR029.14/AA18

**Topic:** H.10. Human Learning and Cognition

**Support:** JSPS KAKENHI (22H00502)

**Title:** Applying the Bayesian estimation model of human timing to virtual baseball batting

**Authors: *Y. TANAKA**[1], R. IMAI[2], J. SUZUKI[2], S. KONISHI[2], C. KASEGAWA[1], M. MIYAZAKI[2], T. KIMURA[3];
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**Abstract:** Psychophysical studies have indicated that the Bayesian estimation operates in timing tasks. That is, the brain utilizes the prior distribution (mean and variance) of target timing to optimize the task performance. In this study, we investigate the applicability of the Bayesian estimation model to the timing behavior in virtual baseball batting. Participants performed ball-speed judgment and batting tasks in a virtual batting system. Each participant completed 240 trials of each task. The time interval from the pitching of the ball to the ball reaching the home base was sampled from short-time prior (500-1000 ms, i.e., fastball) or long-time prior (1000-1500 ms, i.e., slowball). Each prior was assigned to the trials 1-120 or 121-240. In the ball-speed judgment task, the participants judged whether the current pitched ball was faster or slower than the average ball speed in the first sessions (20 trials), for each prior. The precision of the speed judgment was lower for the long-time prior than for the short-time prior, which was consistent with the scalar variability theory. In the batting task, the participants swinged a virtual bat to hit the pitched ball. The results showed that the batting timing was biased toward the respective means of the priors ("central tendency"), which was consistent with the basic Bayesian estimation model. However, the central tendency was smaller for the long prior than for the short prior, which was contrary to the prediction of the Bayesian estimation model, including the effects of scalar variability. Notably, the participants report that, in the batting task, they observed the slowballs (long-time prior) until just before they reach the home base. Under this strategy, the estimation of time intervals becomes shorter, which results in smaller scalar variability. The smaller scalar variability induces a smaller central tendency, according to the Bayesian estimation model. This suggests that we should consider such task strategies when applying the Bayesian estimation model to daily behavior with greater degrees of freedom than that in simple psychophysical tasks.

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**Poster**

**PSTR029. Timing and Temporal Processing I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR029.15/AA19

**Topic:** H.10. Human Learning and Cognition

**Support:** JSPS KAKENHI (22H00502)
JSPS KAKENHI (19H01087)
JSPS KAKENHI (17K K0004)

**Title:** Selective assignment of supplementary vocalization facilitates the acquisition of multiple prior distributions in human coincidence timing

**Authors: *Y. OKUMURA**[1], S. NATSUME[2], H. MIWA[1], J. HERON[3], N. W. ROACH[4], M. MIYAZAKI[1,2];
[1]Fac. of Informatics, Shizuoka Univ., Hamamatsu, Japan; [2]Grad. Sch. of Integrated Sci. and Technol., Hamamatsu, Japan; [3]Sch. of Optometry and Vision Sci., Univ. of Bradford, Bradford, United Kingdom; [4]The Univ. of Nottingham, The Univ. of Nottingham, Nottingham, United Kingdom

**Abstract:** During sensorimotor tasks, the brain can learn regularities in target stimuli and exploit this prior knowledge to optimize task performance. Because events with different statistical properties can occur in natural environments (e.g., fastball/slowball in baseball batting), it is critical that multiple prior distributions can be learned and retained. Our research group previously found that when two prior distributions are assigned to different body parts to make timing responses, participants concurrently acquired both priors (Matsumura et al., FENES2020). However, in complex environments, linking every prior to a distinct body part is likely to become impractical. In the current study, we focused on supplementary vocalization that is often observed in sports. Participants (n = 36) performed a coincidence timing task in which three sequential visual stimuli (S1, S2, and S3) were presented to the right or left of a fixation point. The time interval between S1 and S2 was equal to that between S2 and S3 in each trial. Participants attempted to press a handheld button with their dominant thumb such that its onset coincided with that of S3. Stimulus intervals presented on the left and right were randomly sampled from either a short (500-980 ms) or long (1100-1580 ms) prior distribution. Participants were divided into three groups: the *all-vocalization* group voiced the syllable “Ba” in time with every button press response; the *selective-vocalization* did so only when stimuli were presented on one side of fixation (corresponding selectively to either the short or long prior); whereas the *non-vocalization* group always pressed the button without vocalization. Participants’ response timings were fitted with a Bayesian estimation model, allowing evaluation of the differences between the priors acquired for each interval distributions. Results showed greater separation between prior means in the selective-vocalization group, suggesting that selective assignment of supplementary vocalization can facilitate concurrent acquisition of multiple prior distributions.

**Disclosures: Y. Okumura:** None. **S. Natsume:** None. **H. Miwa:** None. **J. Heron:** None. **N.W. Roach:** None. **M. Miyazaki:** None.

**Poster**

**PSTR029. Timing and Temporal Processing I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR029.16/AA20

**Topic:** H.10. Human Learning and Cognition

**Title:** Music expectancy improves concurrent visual sequences encoding by providing cross-modal temporal schemas

**Authors: *Y. REN**[1], T. BROWN[2];
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**Abstract:** It is of great interest how background music affects concurrent learning, due to its ubiquitous presence in daily life such as work and study. One mechanism through which it could help relates to the schema theory of memory, which suggests that new information that can be associated with a prior memory structure can be acquired faster. Music, especially familiar music, is a highly predictable sequence of events, with a stable tonal and temporal structure. However, current literature has shown mixed results for how music listening modulates non-text-based information learning. We designed a series of experiments to test whether predictable music, as a form of prior knowledge, can provide a sequential template and help encoding of sequences of other modalities. In our first experiment, we utilized fMRI and tested this possibility via an abstract shape sequence learning task, paired with background music designed with different levels of predictability. Our results showed that visual sequences learned with music had a better memory performance compared to those paired with control isochronous streams. Within music conditions, learning performance was higher for visual sequences learned with regularly-structured and familiar music. fMRI results revealed multiple potential mechanisms for the benefits of music familiarity and regularity: overall, music was associated with decreased activity in the parahippocampal gyrus when encoding visual sequences. Moreover, regularly-structured (predictable, as opposed to violating music syntax) music showed decreased activity in working memory system circuitry and default mode network areas, and there was greater engagement of the reward system during predictive music listening. Importantly, familiar music increased the functional connectivity between prefrontal cortices, the medial temporal lobe, and the striatum, a network important for how prior knowledge supplements new information encoding. We designed a second, ongoing fMRI experiment to 1) replicate the results with more real-world stimuli, and 2) manipulate and model how prediction errors from music structure affect memory encoding. The latter will reveal more about how different types and levels of predictability of music will affect sequential learning. Most importantly, we aim to investigate how reward system and memory system coordinate when sequences of different modality interacts.

**Disclosures:** **Y. Ren:** None. **T. Brown:** None.

**Poster**

**PSTR029. Timing and Temporal Processing I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR029.17/AA21

**Topic:** H.01. Attention

**Support:** National Natural Science Foundation of China, 32000779
National Natural Science Foundation of China, 31861133012
Shanghai Sailing Program, 20YF1422100

**Title:** Dissociated amplitude and phase effects of alpha oscillation in a nested structure of rhythm- and sequence-based temporal expectation

**Authors: *Z. SU**[1,2,3,4], X. ZHOU[4,5,6], L. WANG[2,3,7];
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**Abstract:** Various temporal information in the environment can be used to predict the timing of an upcoming stimulus and promote the perceptual processing of the expected stimulus. Although it has been shown that both rhythm- and sequence-based temporal expectation enhanced perceptual performance, it remains unclear if and how the nested structure of temporal expectation can benefit perceptual performance. To answer this question, here a nested structure of temporal expectation was constructed to show how the visual perception of the expected stimulus was modulated when the stimulus was predicted by either the low-frequency rhythm, the sequence, or a combination of the two. Meanwhile, the electroencephalographical (EEG) signals were also recorded to examine if different forms of temporal expectation were underlined by distinct neural mechanisms.
In combination with a Drift Diffusion Model (DDM), the behavioral data showed that the rhythmic and sequence information additively increased the accumulation speed of the sensory evidence and lowered the decision threshold. The EEG results showed that the neural activity in the visual cortex was entrained by the low-frequency rhythms and the entrained neural oscillation persisted even after the cessation of the rhythmic stream. Importantly, the amplitude and the phase of the pre-stimulus alpha activity showed distinct roles. The alpha amplitude was mainly modulated by the rhythmic information, with fluctuations in alpha amplitude aligned to the phase of the entrained low-frequency oscillation (i.e., strong phase-amplitude coupling). Moreover, the trial-by-trial perceptual processing could be predicted by the rhythm-modulated alpha amplitude. The alpha phase, on the other hand, was modulated by both rhythm- and sequence-based expectations, with increased inter-trial coherence of the alpha phase in response to both rhythmic and sequence information. The combination of rhythm-based and sequence-based expectations effectively biased the alpha phase to an optimal phase, promoting the perceptual processing of the expected stimulus.
Overall, the findings suggested that multiscale brain oscillations, such as entrained low-frequency rhythms and alpha oscillations, are coordinated to modulate the visual perception in a nested structure of temporal expectation.

**Disclosures: Z. Su:** None. **X. Zhou:** None. **L. Wang:** None.

**Poster**

**PSTR030. Cross-Modal Processing: Neural Circuitry and Development**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR030.01/AA22

**Topic:** D.08. Multisensory Integration

**Support:** NSF Grant BCS-1756313

**Title:** A direct connection from auditory to visual word form areas bridges the auditory and written speech networks: evidence from fMRI and MEG connectivity

**Authors: *L. CHANG**[1], P. CHO[3], S. DAMERA[1], K. JIN[2], K. M. GATES[4], L. E. BERNSTEIN[5], M. RIESENHUBER[1];
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**Abstract:** Models for reading include the "visual word form area" (VWFA) in the lateral occipital temporal cortex that has demonstrated neural selectivity for written words (Glezer et al., Neuron, 2009; Kronbichler et al., Neuroimage, 2004; Lochy et al., PNAS, 2018). However, studies also report that spoken words activated the VWFA (Price & Devlin, Trends Cogn Sci, 2011; Cohen et al., Neuroimage, 2004; Dehaene et al., Science, 2010), suggesting a possibility that the auditory speech network provides input to the VWFA. However, connectivity between the written and auditory speech networks remains understudied. Here, we test whether the two systems are connected either by 1) a direct connection between the VWFA and the auditory word form area (AWFA), an analogous spoken word lexicon to the VWFA in the mid-anterior superior temporal gyrus (Damera et al., Neurobiol Lang, 2023), or 2) an indirect connection from the AWFA to the inferior frontal cortex (IFC), an area associated with higher-order processing for written and auditory speech (Pugh et al., J Commun Disord, 2001; Rauschecker & Scott, Nat Neuro, 2009; Hickok & Poeppel, Nat Rev Neurosci, 2007), then to the VWFA. We first examined the functional connectivity (FC) between individually-defined ROIs for the VWFA, AWFA, and IFC (N=35) during spoken word processing and found significant positive FC (AWFA<->VWFA, VWFA<->IFC, AWFA<->IFC: all $p<0.001$). To delineate these connections more precisely and gain insight into directionality and timing, we re-analyzed the MEG data from the Mother of all Unification Studies database (MOUS; Schoffelen et al., Sci Data, 2019) and used beamforming to calculate signal coherence (N=95) between anatomically-restricted group ROIs derived from the averaged coordinates of the individually-defined ROIs. This identified significant low-frequency coherence between the AWFA and VWFA ($p<0.005$; starting at 20ms for 6Hz and 42.5ms for 8Hz), but, crucially, not between the IFC and AWFA or the IFC and VWFA. Activation time courses also supported a direct interaction between AWFA and VWFA rather than an indirect route via the IFC. An effective connectivity analysis using Group Iterative Multiple Model Estimation (GIMME; Lane & Gates, Struct Equ Modeling, 2017) confirmed the AWFA->VWFA connectivity in a majority of participants at the individual-subject level and also provided evidence that the VWFA<->IFC correlation reflected input from the VWFA to the IFC rather than top-down input. These results provide evidence for a direct

connection between the AWFA to the VWFA that interfaces the auditory "what" stream with the reading network. This direct connection could be instrumental in shaping the VWFA.

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**Poster**

**PSTR030. Cross-Modal Processing: Neural Circuitry and Development**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR030.02/AA23

**Topic:** D.08. Multisensory Integration

**Support:** DFG 368482240/GRK2416

**Title:** Modality specificity of multisensory integration and decision-making in frontal cortex and superior colliculus

**Authors: *A. DESPATIN**[1,2], S. GRAFF[1,2], I. LENZI[1,2], K. DOERENKAMP[1], G. NABBEFELD[1], M. L. PÉREZ[1], A. JAIN[1,2], S. GRÜN[2], B. KAMPA[1], S. MUSALL[1,2]; [1]RWTH Aachen Univ., Aachen, Germany; [2]Forschungszentrum Jülich, Jülich, Germany

**Abstract:** The integration of sensory inputs from different senses is a crucial aspect of sensory perception and the production of corresponding behavioral decisions. However, whether such multisensory integration occurs at specific stages of neural processing, for example after initial processing of unisensory information but preceding the formation of a behavioral choice, remains unclear. Two brain regions, the anterolateral motor cortex (ALM) and the superior colliculus (SC) have been implicated as important structures for both multisensory integration and decision-making, suggesting that they are part of a cortico-subcortical loop that transforms multisensory inputs into behavioral decisions. To study the role of these areas in multisensory integration and decision-making, we trained mice in a multisensory discrimination task, where animals had to integrate visual and tactile information over time to identify the target stimulus side. We then performed simultaneous neural recordings in ALM and SC, using high-density Neuropixels probes, in task-performing animals. We found robust visual and tactile responses in ALM and SC, with a clear separation of modalities between superficial and deep SC layers (dSC). To ensure that multisensory responses were not driven by correlated movements, we used a generalized linear model that included rich behavioral information to separate stimulus-related from movement-related neural activity. Aside from sensory responses, both ALM and dSC showed strong choice-predictive activity during stimulus presentation and a subsequent delay period. Interestingly, visual and tactile choices were differently encoded in ALM, with no clear relation between visual and tactile choice neurons. Moreover, neurons that encoded multisensory choices were clearly distinct from unisensory choice neurons. In contrast, dSC neurons encoded choice signals independently of the sensory modality. To causally confirm these results, we performed optogenetic inactivation in each area during simultaneous Neuropixels recordings.

Optogenetic inactivation of both ALM and dSC strongly reduced animals' choice performance during the stimulus and delay period and disrupted choice-related dynamics in both regions. This suggests a hierarchical transformation of multisensory information into behavioral decisions, where the SC sends multisensory information to ALM, which creates modality-specific decisions that are then returned to the SC to create motor outputs.

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**Poster**

**PSTR030. Cross-Modal Processing: Neural Circuitry and Development**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR030.03/AA24

**Topic:** D.08. Multisensory Integration

**Support:** National Research Foundation of Korea funded by the Ministry of Science & ICT Grant NRF-2021R1A2C3012159
Institute for Basic Science Grant IBS-R002-A2

**Title:** Weakening of the cortical inputs to the posterior parietal cortex in the Shank3$^{\Delta 14\text{-}16}$ mice

**Authors: *S.-M. OH**;
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**Abstract:** Dysfunction in sensory processing and multisensory integration is often observed in patients with autism spectrum disorder (ASD). Deletion in the Shank3 gene is well-known to cause autistic phenotypes in both humans and mice. However, it is still unclear whether and how Shank3 deficiency causes changes in anatomical and functional connectivity in the cortical areas that process and integrate sensory information. One of the key area that is important for sensory processing, integration, and decision making is the posterior parietal cortex (PPC). Therefore, we examined the cortical projections to the posterior parietal cortex (PPC) throughout the brain in Shank3 deleted (Shank3$^{\Delta 14\text{-}16}$) mice. We first characterized distinct connectivity patterns within the PPC subareas defined by the medial-to-lateral (ML) axis. We found that the anterior visual area (VISa), the middle part of the PPC, receives dense and balanced inputs from both frontal and sensory areas. We further found that these inputs were significantly reduced in the Shank3$^{\Delta 14\text{-}16}$ mice. Next, we used the wide-field calcium imaging and measured functional connectivity between VISa and other cortical regions. We found a significant reduction in the calcium activity correlation between retrosplenial area (RSP) and PPC in Shank3$^{\Delta 14\text{-}16}$ mice. Collectively, our data demonstrate that anatomical and functional connectivity is weakened in the posterior parietal cortex in Shank3$^{\Delta 14\text{-}16}$ mice.

**Disclosures: S. Oh:** None.

**Poster**

**PSTR030. Cross-Modal Processing: Neural Circuitry and Development**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR030.04/AA25

**Topic:** D.08. Multisensory Integration

**Support:** Swiss National Science Foundation Grant PCEFP3_181070

**Title:** Cortical circuits for cross-modal transfer learning

**Authors: M. GUYOTON**, *G. MATTEUCCI, G. FOUCHER, S. EL-BOUSTANI;
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**Abstract:** The ability to combine sensory signals from different modalities is essential for effective behavior. In mice, tactile sensations from their whiskers are combined with visual information to identify objects or navigate their environment. To test the hypothesis that these sensory systems share common inputs and could potentially share a similar functional organization in the cortex that could be used to translate information from one system to another, we trained water-restricted animals to discriminate between stimulations of top and bottom whiskers during goal-directed behaviors. After becoming experts, we suddenly replaced the tactile stimuli with top and bottom visual cues on a screen. When stimuli from different modalities were congruent in space, mice were able to instantaneously transfer knowledge from one task to another without affecting overall performance. However, when the rule was reversed, and incongruent stimuli were rewarded after transfer, mice failed to solve the task. Using multi-scale imaging tools and anatomical approaches, we characterized visuo-tactile integration in the mouse cortex. Transgenic mice expressing GCaMP6f in cortical layer 2/3 were implanted with a cranial window offering a wide optical access to primary and associative sensory cortices. Animals were imaged while being presented tactile, visual, or combinations of visuo-tactile stimuli spanning the vertical axis. We identified two associative areas subject to visuo-tactile integration belonging to the ventral and dorsal streams, respectively. Topographical mapping of tactile and visual stimulations in these areas was aligned along the vertical axis and evoked multisensory interactions. When visuotactile combinations were congruent in space, neuronal responses were enhanced compared to unisensory responses. Finally, targeted expression of tetanus toxin light chain in visuotactile associative regions using viral vectors effectively suppressed activity in these areas before behavioral training. This led to a drastic drop in performance during transfer learning, showing the critical role of these areas for cross-modal transfer learning.

**Disclosures: M. Guyoton:** None. **G. Matteucci:** None. **G. Foucher:** None. **S. El-Boustani:** None.

**Poster**

**PSTR030. Cross-Modal Processing: Neural Circuitry and Development**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR030.05/AA26

**Topic:** D.08. Multisensory Integration

**Support:** NIH Grant F31AG077797
NIH Grant K99MH10138
NIH Grant P51OD011107

**Title:** Multimodal characterization of the macaque insula in vivo

**Authors: *J. A. CHARBONNEAU**[1,2], E. P. RAVEN[3], Y. KATSUMI[4], E. BLISS-MOREAU[5,2]; [1]Neurosci. Grad. Program, [2]California Natl. Primate Res. Ctr., Univ. of California Davis, Davis, CA; [3]Radiology, New York Univ., New York, NY; [4]Neurol., Harvard Med. Sch. and Massachusetts Gen. Hosp., Charlestown, MA; [5]Psychology, Univ. of California, Davis, Davis, CA

**Abstract:** The primate insula is a heterogeneous region implicated in a variety of functions including basic energy regulation, sensorimotor integration, and the generation of a sense of self. Knowledge about insula structure and function comes primarily from two sources: (1) human *in vivo* neuroimaging data and (2) non-human primate (primarily macaque monkey) *post mortem* histological data. Functional imaging of the human insula shows that this region is nearly ubiquitously activated across task domains and is a hub in a domain-general functional network supporting predictive bodily regulation and the brain's modeling of its sensory consequences (i.e., the interoceptive-allostatic network). Meta-analyses of task-based and resting state functional imaging work alike suggest that the human insula can be reliably divided into 3-4 functional subregions: one each for socioaffective, chemosensory, sensorimotor, and cognitive processing, although each with substantial overlap and coactivation. Histological assessment of the macaque insula shows that the insula can be divided into 3 cytoarchitectural subregions (i.e., granular, dysgranular, and agranular) and tract tracing experiments demonstrate that these subregions have varying connectivity with the rest of the cerebral cortex and subcortex. In order to build a translational bridge between the wealth of human neuroimaging data on the insula and the highly detailed histological data available on the macaque insula, we characterized the macaque insula *in vivo* using the same tools available for human research—resting state functional MRI (fMRI) and diffusion MRI (dMRI). We collected fMRI and dMRI data from N=19 group-raised and group-living male rhesus macaques (*Macaca mulatta*). Using nominal clustering techniques, we demonstrated that resting state fMRI of the macaque insula suggests the presence of 3 clusters similar to those suggested for the human insula. We also demonstrated that the organization of intra-insular functional connectivity can be described as hierarchical gradients primarily along an anterior-posterior axis and secondarily along a dorsal-ventral axis, which appear to be consistent with gradients of cytoarchitectural features previously established using histology. Analyses of diffusion data suggested convergent results with the functional data. Taken together, our data suggest that the macaque is a good model for studying human insula function and opens the possibility for translational studies further characterizing the structure of

the macaque insula and directly relating *in vivo* and histological measures in ways that human studies cannot.

**Disclosures: J.A. Charbonneau:** None. **E.P. Raven:** None. **Y. Katsumi:** None. **E. Bliss-Moreau:** None.

**Poster**

**PSTR030. Cross-Modal Processing: Neural Circuitry and Development**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR030.06/AA27

**Topic:** D.08. Multisensory Integration

**Support:** P51OD011092
R01NS093998

**Title:** Implicit learning and suppression of visual cortex responses during trace conditioning under anesthesia in rhesus macaques

**Authors: M. M. CHERNOV**, P. AUDURIER, D. S. JACOBS, *V. D. COSTA, R. M. FRIEDMAN;
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**Abstract:** Learning and memory enables organisms to make predictions about the outcomes associated with specific stimuli. While anesthesia prevents the formation of explicit memories, it does not prevent implicit memory formation (Samuel et al., 2018). The neural mechanisms underlying implicit learning and memory formation under anesthesia are understudied, especially for learning and memory of multisensory associations. We recorded neural activity in early visual cortex of two rhesus macaques under propofol anesthesia in order to determine how neuronal responses are modulated during a trace conditioning procedure in which visual stimuli (CS) were probabilistically associated with delayed somatosensory stimulation of the fingers (US). One set of visual cues was associated with a high probability of somatosensory stimulation while the other was associated with a low probability. Pupillometry was used to verify that conditioned associations were learned under anesthesia. Visual cues associated with a higher likelihood of somatosensory stimulation elicited increased pupil dilation. Implicit learning was also evident in the responses of visual cortical neurons. In a subset of the neurons recorded from areas V2 or V4, activity was suppressed immediately following the offset of a visual cue that predicted that somatosensory stimulation was likely ($p(US) = 0.75$), up until receipt of somatosensory stimulation. Similar suppression of early visual cortical responses was not observed following the offset of visual cues that predicted somatosensory stimulation was unlikely ($p(US) = 0.25$). During trace conditioning we used a linear classifier to accurately decode from population activity in early visual cortex, both the predictability of the conditioned stimulus and the receipt of somatosensory stimulation. These results imply that under anesthesia implicit multisensory associations can modulate early visual cortical responses. These findings

have practical implications for understanding how implicit learning and memory formation occur under anesthesia and potentially leads to negative outcomes following anesthetic events.

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**Poster**

**PSTR030. Cross-Modal Processing: Neural Circuitry and Development**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR030.07/AA28

**Topic:** D.08. Multisensory Integration

**Title:** Intracortical and thalamocortical crossmodal plasticity within the audiovisual cortex following partial hearing loss in adulthood

**Authors: *A. SCHORMANS**[1], B. L. ALLMAN[2];
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**Abstract:** Partial hearing loss in adulthood is known to induce crossmodal plasticity in the audiovisual cortex, which is characterized by an increased proportion of neurons now overtly responsive to visual stimulation. In the present study, we used a rat modal to investigate whether this hearing loss-induced crossmodal plasticity manifests solely from intrinsic changes in the audiovisual cortex itself, or via a combination of intracortical and thalamocortical effects. In Experiment 1, adult rats were exposed to loud noise and two weeks later, laminar electrophysiological recordings were performed in their audiovisual cortex before and after pharmacological cortical silencing to ultimately examine the thalamocortical contributions to crossmodal plasticity. Using current source density analysis of the local field potential (LFP) data, we observed that, noise exposure enhanced the visual-evoked activity solely within the granular layer of the audiovisual cortex, indicative of an increase in visual-evoked thalamocortical input. Despite this increased visual input, there was no change in the overall strength of the postsynaptic activity between the control and noise-exposed groups, suggesting that there was a re-allocation of inputs post-noise exposure. In Experiment 2, we investigated whether the increase in visual responsiveness following noise exposure occurs, at least in part, because of pre-existing anatomical connections becoming unmasked by the resultant acoustic deprivation. To that end, we used an epidural electrode array that spanned the higher-order sensory cortices, and compared the visual-evoked LFP responses before- and immediately after loud noise exposure in the same adult rats. As predicted, noise exposure resulted in a loss of auditory responsiveness across all sound intensities, as well as an immediate manifestation of crossmodal plasticity—characterized as an increase in visual-evoked amplitudes and a decrease in response latency—across all recording sites. Interestingly, the rapid emergence of crossmodal plasticity appeared to be dependent on the intensity of the visual stimulation, as the brighter the visual stimulus, the greater the relative change from baseline following hearing loss. Taken

together, our collective results have shown that noise-induced crossmodal plasticity alters thalamocortical processing of visual stimuli and emerges immediately following acoustic trauma within the higher-order sensory cortices; findings in support of the working hypothesis that crossmodal plasticity manifests, at least in part, by the unmasking of pre-existing anatomical connections.

**Disclosures: A. Schormans:** None. **B.L. Allman:** None.

**Poster**

**PSTR030. Cross-Modal Processing: Neural Circuitry and Development**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR030.08/BB1

**Topic:** D.08. Multisensory Integration

**Support:** JST CREST (grant numbers JPMJCR1755 and JPMJCR22P6 to H.W.).

**Title:** Neuronal circuite for multisensory integration in higher visual cortex

**Authors: *M. INOUE**[1], Y. TANISUMI[1,3], A. HASHIMOTO[1], *M. INOUE[2], I. TAKEDA[1,3], D. KATO[1,3], H. WAKE[1,3];
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**Abstract:** Multisensory integration is a sensory processing mechanism that integrate input information from different sensory modalities, occurring during sensory reception and perception. Previous study showed that the anterolateral visual area (AL) plays a pivotal role to response audio-visual stimuli compared to the primary visual or auditory area. Another study proved AL neurons showed stronger response in tasks requiring integration of multisensory inputs compared to other secondary visual cortexes. Given the role of AL in sensory integration, this study focused on the multisensory information processing mechanisms that receive and integrate sensory information in AL. We first detected cortico-cortical projection from the primary sensory cortexes (S1BF, V1, and A1) to AL using anterograde and retrograde labeling. Also, we used eGRASP technique to visualize the synaptic connections from these primary sensory cortexes to AL. We revealed the axonal projection and synaptic connection between these cortico-cortical pathways, suggesting that AL directly receive sensory inputs from the multisensory primary cortexes. The neuronal responses in AL to sensory input (whisker stimulation, visual and auditory representation) by *in vivo* $Ca^{2+}$ imaging detected neuronal populations that respond to single or multiple sensory inputs. We found that some AL neurons responded to only a single sensory stimulus, while others responded only when presented with multiple sensory stimuli. To determine the function of these neurons, we analyzed neuronal activities during the multisensory discrimination task. Moreover, we are trying to elucidate the role of multisensory responded neurons by correlating the these neuronal activity induced by holographic stimulation with the mice behavior.

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**Poster**

**PSTR030. Cross-Modal Processing: Neural Circuitry and Development**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR030.09/BB2

**Topic:** D.08. Multisensory Integration

**Support:** NIH Grant U19MH114830

**Title:** Refined cortical-cortical and cortical-subcortical connectomes of somatosensory cortex at a level of single full morph cells

**Authors: *Y. WANG**[1], H.-C. KUANG[1], X. KUANG[2], L. NG[1], S. YAO[1], P. LESNAR[1], Y. LI[2], L. EL-HIFNAWI[1], N. CHEN[1], J. CHANDRASHEKAR[1], C. FARRELL[1], T. KARLSSON[1], B. SUTTON[1], R. DALLEY[1], G. WILLIAMS[1], J. ANDRADE[1], A.-A. LI[3], H. GONG[3], Q. LUO[3], S. SORENSEN[1], H. ZENG[1];
[1]Allen Inst., Seattle, WA; [2]Wenzhou Med. Univ., Wenzhou, China; [3]Huazhong Univ. of Sci. and Technol. (HUST), Wuhan, China

**Abstract:** Somatosensory (SS) cortex and projections play a critical role in processing sensory information related to touch, temperature, pain, and body position, which consists of seven primary and one secondary subregions. Researchers have explored the architecture and organization of these projections using various techniques, but a whole-brain level study of single full morph cells has not been conducted until now. In this study, we performed computation-assisted reconstructions to obtain full morph dendrites and axons of single neurons across different regions in the SS cortex using Vaa3D-TeraVR from a whole brain image stack acquired with a two-photon fluorescence micro-optical sectioning tomography system (2p-fMOST). Neurons were sparsely labeled using tamoxifen-inducible Cre driver lines crossed to a bright GFP reporter. Reconstructed from different layers of all eight subregions in SS cortex, the full morph cells were classified based on combined transcriptomic and morphological features. The cortical-cortical (CC) and cortical-subcortical (C-subC) connectomes of different SS cell types were quantitatively analyzed in terms of clustering analysis, targeting probability and targeting strength, and further compared with the connectomes detected by commonly used bulk injections. Laminar distributions of axonal projections of individual cell types were also performed for dominant cortical targeting regions. Multiple organization principles of neuronal network were refined at a single cell level, shedding new light on the organization and function of CC and C-subC connectomes of SS cortex. Moreover, limitations of bulk injections were revealed in detecting projection targets in the studied neuronal connectomes, which may have implications for future research.

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**Poster**

**PSTR030. Cross-Modal Processing: Neural Circuitry and Development**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR030.10/BB3

**Topic:** D.08. Multisensory Integration

**Support:** Grand-in-Aid for Transformative Research Areas (A)(21H05688)

**Title:** The role of astrocytes in V2L neuronal remodeling following vision loss

**Authors:** ***I. TAKEDA**[1,2], I. TAKEI[1], M. INOUE[1], A. HASHIMOTO[1], H. WAKE[1,2];
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[2]Div. of Multicellular Circuit Dynamics, Natl. Inst. for Physiological Sci., Okazaki/Aichi, Japan

**Abstract:** In humans, vision loss has divergent effects on broader sensory perception depending on its age of onset. Before puberty, it enhances tactile acuity (cross-modal plasticity), whereas in adulthood, it causes visual illusions. In our previous study (Hashimoto et al., 2023 Cell Reports), we observed a similar phenomenon in mice subjected to monocular vision deprivation (MD) at different ages. MD in 2-week-old mice, akin to partial vision loss in childhood, improved learning rates in a whisker-based discrimination task (cross-modal plasticity). In contrast, MD in 5-week-old mice, akin to partial vision loss in adulthood, conferred no similar benefit. The improvement in 2-week-old MD mice was associated with increased inhibitory synapse stripping resulting in heightened neuronal activity in the secondary visual cortex (V2L) during whisker stimulation. Microglia, through their enwrapping of neuronal somas, were mechanistically responsible, as confirmed by the prevention of these phenomena through microglia ablation. In the present study, we investigate mechanisms of plasticity in adulthood in more detail. We use a more severe model of binocular vision deprivation (BD) in 5-week-old mice, akin to complete blindness in adulthood. In 5-week-old BD mice, neuronal activity with or without whisker stimulation in V2L is reduced but its synchronicity is increased. Furthermore, this is associated with changes in V2L astrocyte physiology with their numbers, $Ca^{2+}$ activity and synchronicity all increasing. RNA sequencing also reveals up-regulated $GABA_A$ receptor-related genes which could facilitate these $Ca^{2+}$ influx-related changes in astrocytes. Taken together, the results of these two studies suggest that microglia and astrocytes facilitate different types of neuronal circuit rewiring. Moreover, their differential recruitment by similar stimuli is age dependent - microglia in childhood, astrocytes in adulthood. Thus, glial cells may play a pivotal role in the age-related divergence in the phenotypes resulting from vision loss-induced circuit remodeling.

**Disclosures:** **I. Takeda:** None. **I. Takei:** None. **M. Inoue:** None. **A. Hashimoto:** None. **H. Wake:** None.

**Poster**

**PSTR030. Cross-Modal Processing: Neural Circuitry and Development**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR030.11/BB4

**Topic:** D.08. Multisensory Integration

**Title:** The evolution of cortical fields in mammals: A comparative analysis of cortical organization in a broad range of mammals including chiroptera, marsupiala, rodentia, afrosoricida, scandentia, erinaceidae and eulipotyphyla

**Authors: *J. LC**[1], L. KRUBITZER[2], S. P. WILSON[3];
[1]Psychology, Univ. Of California Davis Neurosci. Grad. Program, Davis, CA; [2]Ctr. for Neurosci., Univ. of California, Davis, Davis, CA; [3]Pscyhology, Sheffield University, Self-Organization Lab., Sheffield, United Kingdom

**Abstract:** Comparative studies provide important insights into general features of brain organization as
well as features that are derived evolutionarily. These derivations in brain organization are due to specialized adaptations in body morphology, behavior and lifestyle. In the current study, we quantified aspects of cortical organization across a number of major mammalian lineages: 2 species of Chirpotera (bats), 5 species of Marsupiala (marsupials), 9 species of Rodentia (rodents), and 4 species from other orders. These species have a broad range of unique morphological specializations and engage in a variety of behaviors including swimming, burrowing, and climbing. For all species examined, the cortex was pealed from the brainstem and thalamus, manually flattened between glass slides, and cut tangentially on a freezing microtome. Tissue was then processed for myelin and cytochrome oxidase. For most species we examined 3 different individuals, but in some cases, our numbers were limited to 1 or 2 individuals. We performed a microscopic analysis of the entire series of sections from each brain in the collection and drew the boundaries of cortical fields. We limited our analysis to cortical fields whose boundaries could be clearly identified such as primary and secondary visual areas (V1 and V2), primary and second somatosensory areas (S1, S2), auditory cortex, motor cortex and divisions of posterior parietal cortex. Next, we digitized the data to allow for quantification of the size of neocortex and pyriform cortex, and for cortical field size and shape. We then collected information on relevant aspects of lifestyle such as mode of locomotion (e.g. swimming, climbing), diel patterns, and morphological specializations (e.g. specialized digits, wings, whiskers) for correlation with our results on cortical field quantification. This study allows us to appreciate similarities and differences across orders and within orders that correlate with morphological specializations, aspects of lifestyle and even rearing conditions. Finally, we report progress on a novel analysis technique, in which multi-layered perceptrons were trained to classify the area identity at each location on the cortical sheet, simultaneously

for the arealization patterns of multiple species. This technique allows us to investigate the structure and complexity of gene networks involved in arealization, and to interpolate between the arealization patterns of different species, with a view to establishing how these patterns have evolved and might continue to evolve.

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**Poster**

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**Topic:** D.08. Multisensory Integration

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**Title:** Making sense of the internal senses-a multidimensional coding architecture of the vagal interoceptive system

**Authors: *Q. ZHAO**[1,2], C. YU[2], R. WANG[2], Q. XU[2], R. DAI PRA[2], L. ZHANG[4], R. CHANG[3]; [1]Dept. of Neurosci., Yale Univ., New Haven, CT; [2]Dept. of Neurosci., [3]Dept. of Neuroscience; Dept. of C&M Physiol., Yale Sch. of Med., New Haven, CT; [4]Yale Sch. of Medicine, Dept. of Neurol., New Haven, CT

**Abstract:** Understanding our body's internal state is a fundamental life-ensuring process vital for regulating physiological homeostasis, fueling our motivations, and shaping our thoughts and emotions. At the core of this intricate body-brain connection lies the vagal interoceptive system—a crucial axis responsible for transmitting a myriad of signals from the respiratory, cardiovascular, gastrointestinal (GI), endocrine, and immune systems to the brainstem. However, how the vagal interoceptive system is organized to present numerous and diverse body signals to the brain remains shrouded in mystery. In this study, we aim to unravel the underlying coding strategy employed by the vagal sensory neurons (VSNs), focusing on three pivotal physiological features of interoceptive signals: the visceral organ, tissue layer, and stimulus modality. Through extensive single-cell profiling of VSNs from seven major organs using advanced multiplexed organ-barcodes, a remarkable "visceral organ" dimension emerges. This dimension comprises

differentially expressed gene modules that intricately encode VSN target organs along the body's rostral-caudal axis. Intriguingly, our investigation uncovers another "tissue layer" dimension, characterized by distinct gene modules that encode the precise ending locations of VSNs along the organ's surface-lumen axis. Using calcium imaging-guided spatial transcriptomics, we show that VSNs are organized into functional units to sense similar stimulus modalities across organs and tissue layers, constituting a third 'stimulus modality' dimension. The three independent feature-coding dimensions together specify many parallel VSN pathways in a combinatorial fashion and facilitate complex VSN projection in the brainstem. Together, our study highlights a novel multidimensional coding architecture of the mammalian vagal interoceptive system for effective signal communication.

**Disclosures:** **Q. Zhao:** None. **C. Yu:** None. **R. Wang:** None. **Q. Xu:** None. **R. Dai Pra:** None. **L. Zhang:** None. **R. Chang:** None.

**Poster**

**PSTR030. Cross-Modal Processing: Neural Circuitry and Development**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR030.13/BB6

**Topic:** D.08. Multisensory Integration

**Support:** NIH Grant 1R03AG075644-01A1

**Title:** A novel excitatory neuron subclass in the claustrum of the short-tailed fruit bat, Carollia perspicilata, defined by latexin and calretinin labeling.

**Authors:** T. MORELLO, R. KOLLMAR, M. STEWART, ***R. ORMAN**;
SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY

**Abstract:** Latexin is an intracellular marker that has been well-defined in claustrum and dorsal endopiriform nucleus of multiple species. In claustrum and endopiriform nucleus of rat and bat, co-expression of latexin with markers of inhibitory neurons has never been reported, suggesting that the latexin immunoreactive neurons of these regions are excitatory neurons. Calretinin is a calcium binding protein, which, along with parvalbumin and calbindin, is traditionally used to describe subpopulations of interneurons producing GABA throughout the brain, including inhibitory neurons in claustrum and endopiriform nucleus. The distribution of calretinin labeling has also been helpful in describing the boundaries of claustrum in several species. Claustrum is composed of multiple subregions, including the most commonly described "core" and "shell" subregions, each with differing levels of immunoreactivity for calretinin and for latexin. In describing the relationship between the distributions for latexin and multiple calcium binding proteins, we found that there was a small subset of claustral neurons that were immunoreactive for both latexin and calretinin, specifically in the shell region of claustrum. We conclude that the calretinin + / latexin + cells are an excitatory cell subpopulation in the claustrum of the bat, i.e.,

there are at least two different kinds of excitatory cells in claustrum (latexin+/calretinin- and latexin+/calretinin+).

**Disclosures:** **T. Morello:** None. **R. Kollmar:** None. **M. Stewart:** None. **R. Orman:** None.

**Poster**

**PSTR030. Cross-Modal Processing: Neural Circuitry and Development**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR030.14/BB7

**Topic:** D.08. Multisensory Integration

**Support:** R01NS116598
JSPS Overseas research fellowship

**Title:** Elucidation of the input circuitry of the deep mouse auditory cortex.

**Authors: *T. SUZUKI**, T. R. OLSEN, A. R. HASENSTAUB;
Otolaryngology-Head and Neck Surgery, UCSF, San Francisco, CA

**Abstract:** Recent studies have revealed that the auditory cortex (AC) not only processes auditory information but is also involved in behavioral output and is modulated by other sensory information. We have previously shown that the mouse AC contains a group of cells that are influenced by visual information [1]. These neurons are mainly found in the deep layers of the auditory cortex. To identify likely sources of this visual information, we aimed to map the areas that project to deep AC, using localized microinjection of retrograde tracers using iontophoresis. Four C57/BL6 mice (Age at injection: P49-83) were injected with a viral mixture of AAV2retro-hsyn-EGFP and AAV9-hsyn-ChR2-mCherry in the right auditory cortex (Depth: -0.75mm) by iontophoresis injection. After 3-4 weeks, we perfused their brains and then sliced them. EGFP-positive cells were analyzed using Aligning Big Brains & Atlases (BioImaging And Optics Platform) with reference to the Allen Brain Atlas (2017 CCF v3). EGFP-positive cells were scattered throughout the whole brain, but 96.9% were found in the isocortex. The somatosensory cortex accounted for 15.2% and the visual cortex for 8.52%, while the auditory cortex accounted for 52.7% of the total signal. A closer look at the visual region revealed that while the primary visual cortex (VISp) accounted for 0.55%, EGFP-positive cells were also observed in higher visual cortices. While VISa: 0.93% and VISal: 2.54% were well represented and are located adjacent to the auditory cortex, the regions far from the auditory cortex also showed a certain percentage (VISam: 0.41%, VISpm: 0.15%, VISpor: 1.3%). These results provide evidence that the iontophoresis method can reveal the circuit structure of localized cells in the auditory cortex. The deep layers of the mouse auditory cortex, which have been thought to receive input from the medial higher visual cortex [2], actually receive input, large or small, from each of the visual cortex regions identified in this study.
1. Morrill and Hasenstaub. (2018). Visual Information Present in Infragranular Layers of Mouse Auditory Cortex. *J. Neurosci.* 38, 2854-2862. 2. Banks et al. (2011). Descending projections

from extrastriate visual cortex modulate responses of cells in primary auditory cortex. *Cereb. Cortex* 21, 2620-2638.

**Disclosures:** **T. Suzuki:** None. **T.R. Olsen:** None. **A.R. Hasenstaub:** None.

**Poster**

**PSTR030. Cross-Modal Processing: Neural Circuitry and Development**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR030.15/BB8

**Topic:** D.08. Multisensory Integration

**Support:** R01-DC018790

**Title:** Cross-modal plasticity of the thalamic circuit in adults

**Authors: *G. EWALL**[1], A. LIN[2], R. LEE[1], H.-K. LEE[1];
[1]Dept. of Neuroscience, Mind/Brain Inst., [2]Johns Hopkins Univ., Baltimore, MD

**Abstract:** Loss of vision causes robust plasticity in auditory cortex well into adulthood, but the multimodal structures that might instruct this plasticity remain elusive. For many years, adult plasticity was thought be restricted mainly to cortex, but here we report robust plasticity in higher order and primary auditory thalamus following 6-8 days of dark exposure. Measuring miniature postsynaptic events in slice, we find near complete loss of functional input to higher order auditory thalamus (MGBd) in direct contrast to potentiation of inputs to primary auditory thalamus. These complementary changes suggest that paraleminiscal and leminiscal pathways may act in concert to benefit sensory processing and allow for compensatory plasticity. Further, this work reveals thalamus as an important site of adult plasticity.

**Disclosures:** **G. Ewall:** None. **A. Lin:** None. **R. Lee:** None. **H. Lee:** None.

**Poster**

**PSTR030. Cross-Modal Processing: Neural Circuitry and Development**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR030.16/BB9

**Topic:** D.08. Multisensory Integration

**Support:** ERC Synergy Grant 'BrainPlay - the self-teaching brain'
DFG, German Research Foundation – EXC-2049 – 390688087
Humboldt-Universität zu Berlin

**Title:** A Myelin Map of Trunk Folds in the Elephant Trigeminal Nucleus

**Authors: *N. REVEYAZ**[1], U. SCHNEEWEIß[1], O. HEISE[1], L. V. KAUFMANN[1,2], T. HILDEBRANDT[4], M. BRECHT[1,3];
[1]Bernstein Ctr. For Computat. Neuroscinece Berlin, Berlin, Germany; [2]Berlin Sch. of Mind and Brain, [3]NeuroCure Cluster of Excellence, Humboldt-Universität zu Berlin, Berlin, Germany; [4]Leibniz Inst. for Zoo and Wildlife Res., Berlin, Germany

**Abstract:** Elephants are the largest extant terrestrial animals and rely on their trunks for a series of tasks, mainly to acquire food. While the musculature and its innervation have already been studied, the sensory integration of the trunk in the brain is still poorly understood. The sensory input from the trunk to the brain has to relay to the trigeminal nuclei. Here we study brainstem trunk representations in the elephant trigeminal nuclei. For this purpose, we collected and treated trigeminal nuclei from Asian (*Elephas maximus*) and African (*Loxodonta africana*) Elephants. These samples were cryo-sliced and metabolic staining, antibody staining, or classic histological staining were performed. Following these experiments, we were able to draw several conclusions. The trigeminal nuclei receive dense neurofilament-H positive sensory innervation and form a huge bump on the ventral brainstem, a structure previously referred to as elephant inferior olive. Furthermore, dense vascularization and the most intense cytochrome-oxidase reactivity of all elephant brainstem structures distinguish an elongated putative trunk module. In this module, the neuron density is low and glia outnumbers neurons by ~108:1. The dendritic trees are elongated along the axis of axon bundles (myelin stripes) crossing the trunk module. We show a remarkable correspondence of trunk module myelin stripes to trunk folds in terms of number, orientation, patterning, and species-specific trunk fold differences. We argue stripes represent a myelin map of trunk folds rather than a classic white matter supply system. As myelin stripes have little to no branching in the module, their thickness shows no relation to the number of target neurons. Mapping myelin stripes to trunk folds allows determining neural magnification factors across the module, which change from 1000:1 proximally to 5:1 in the trunk finger. In Asian elephants, magnification analysis reveals an enlargement of the representation of trunk parts, with which Asian elephants wrap objects. We conclude the elephant trigeminal trunk module is exquisitely organized into trunk fold-related submodules. The observation of a myelin map of trunk folds challenges our thinking about white matter function solely in terms of connectivity.

**Disclosures: N. Reveyaz:** None. **U. Schneeweiß:** None. **O. Heise:** None. **L.V. Kaufmann:** None. **T. Hildebrandt:** None. **M. Brecht:** None.

**Poster**

**PSTR030. Cross-Modal Processing: Neural Circuitry and Development**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR030.17/BB10

**Topic:** D.08. Multisensory Integration

**Support:** NIH Grant DC018580
NIH Grant EY032230

**Title:** The role of sensory experience in the development of the auditory spatial topographic map and visuo-auditory integration in the mouse superior colliculus

**Authors: *Y. SI**, B. R. MULLEN, A. M. LITKE, D. A. FELDHEIM;
UC Santa Cruz, SANTA CRUZ, CA

**Abstract:** Localizing an object in a complex environment and instantaneously evaluating its saliency is a fundamental brain function critical for survival. To achieve this, the brain needs to receive, process, and integrate sensory information from various modalities. A model to study spatial sensory integration is the superior colliculus (SC), a midbrain structure that contains aligned spatial maps of visual, auditory, and somatosensory space, and contains multimodal neurons with aligned spatial receptive fields (RFs). The SC then integrates these inputs to promote an appropriate motor response. A combination of graded molecular cues and activity-dependent refinement is used to create the point-to-point map of visual space in the SC. However, it remains unknown how the computed auditory map of space in the SC develops and becomes aligned and integrated with the visual map. Here we describe a set of experiments designed to test the hypothesis that sensory experience is required to align the visual and auditory maps of azimuth in the mouse SC. To test this hypothesis, we have manipulated visual and auditory experience in CBA/CaJ mice and determined the slopes of the visual and auditory SC maps (RF azimuth vs. anteroposterior SC position) using large-scale in vivo physiological recordings of SC neurons in response to spatially restricted visual and auditory stimuli. Our data show that neither retinal input nor visual experience is required for the formation of the auditory topographic map of space in the mouse SC. We do find, however, that auditory experience is required to form a normal auditory map, but not for forming the visual map, leading to their misalignment in the absence of auditory experience. Taken together, these results suggest that the visual map is not used as a template to form an auditory map of space and that auditory but not visual experience is required to form and align auditory and visual maps in the SC.

**Disclosures: Y. Si:** None. **B.R. Mullen:** None. **A.M. Litke:** None. **D.A. feldheim:** None.

**Poster**

**PSTR030. Cross-Modal Processing: Neural Circuitry and Development**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR030.18/BB11

**Topic:** D.08. Multisensory Integration

**Support:** Sinergia grant CRSII5_180316
UZH Forschungskredit grant K-41220-07-01
URPP grant

**Title:** Behavior-relevant top-down cross-modal predictions in mouse neocortex

**Authors: *S. HAN**, F. HELMCHEN;
Brain Res. Inst., Univ. of Zurich, Zurich, Switzerland

**Abstract:** Animals rely on predicting their environment and the consequences of their actions to adapt to a constantly changing world. The predictive coding hypothesis proposes that the brain generates predictions and continuously compares them with bottom-up sensory inputs to guide behavior. However, how the brain reconciles conflicting top-down predictions and bottom-up sensory information during behavior remains unclear. To address this question, we simultaneously imaged neuronal populations in the mouse somatosensory cortex and the posterior parietal cortex during an auditory-cued texture discrimination task. After mice learnt the task with fixed tone-texture matching, mismatched pairing caused conflicting tone-based texture predictions and actual texture inputs. When top-down interaction was dominant, texture representations in both areas were modified and mice decided based on the predicted rather than actual texture, whereas dominant bottom-up interaction corrected the representations as well as behavioral choice. Our findings provide evidence for hierarchical predictive coding in the mouse neocortex and open new avenues for understanding higher cognitive functions.

**Disclosures: S. Han:** None. **F. Helmchen:** None.

**Poster**

**PSTR030. Cross-Modal Processing: Neural Circuitry and Development**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR030.19/BB12

**Topic:** D.08. Multisensory Integration

**Support:** NIH Grant EY031532
Tab Williams Family Foundation

**Title:** Experience develops specific visual-nonvisual multisensory integration capabilities

**Authors:** S. A. SMYRE, N. L. BEAN, B. E. STEIN, ***B. A. ROWLAND**;
Wake Forest Univ. Sch. of Med., Winston Salem, NC

**Abstract:** Using the multisensory neuron in the cat superior colliculus (SC) as a model, we found that the brain develops its ability to integrate visual and non-visual (auditory and/or somatosensory) stimuli during early postnatal life based on experience with specific cross-modal combinations. For example, precluding visual-auditory experience by rearing animals in darkness or omnidirectional masking broadband sound blocks the maturation of visual-auditory integration capabilities. Individual SC multisensory neurons fail to show their characteristic ability to synthesize inputs from congruent visual-auditory cues and thereby enhance their responses. Animals also fail to show normal multisensory performance benefits, retaining the neonatal or “default” computation whereby these sensory inputs inhibit one another. This condition is only modestly ameliorated when such animals are exposed to a normal environment as adults. However, the defect can be overcome via special multisensory training paradigms in

which spatiotemporally congruent visual-auditory stimulus pairs are repeatedly presented at a single location in space. With this exposure, visual-auditory SC neurons whose receptive fields encroach on the exposure location change their multisensory computation from competition to one in which congruent visual-auditory stimuli elicit the enhanced responses typical of the normal brain. These physiological changes are paralleled by changes in behavior: after multisensory training, the detection and localization of congruent visual-auditory pairs are now greatly enhanced at the exposure location. These findings reinforce that multisensory experience is crucial for multisensory development at all ages, and that multisensory training can greatly accelerate this development in adults relative to the uncontrolled multisensory experience offered by normal environments.

**Disclosures: S.A. Smyre:** None. **N.L. Bean:** None. **B.E. Stein:** None. **B.A. Rowland:** None.

**Poster**

**PSTR030. Cross-Modal Processing: Neural Circuitry and Development**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR030.20/BB13

**Topic:** D.08. Multisensory Integration

**Support:** NIH Grant EY026916
Tab Williams Family Foundation

**Title:** Visual Pattern Discrimination After the Rehabilitation of Hemianopia by Cross-Modal Exposure

**Authors: *N. L. BEAN**, B. E. STEIN, B. A. ROWLAND;
Wake Forest Sch. of Med., Winston Salem, NC

**Abstract:** Damage to visual cortex on one side of the brain often induces an enduring blindness on the opposite side of space (“hemianopia”). A cross-modal exposure paradigm involving repeated exposure to spatiotemporally congruent visual-auditory stimuli has been shown to restore the ability to detect and respond to contralesional visual stimuli. The paradigm is believed to reinvigorate visual processing in circuits mediated by the midbrain superior colliculus (SC) by exploiting its capacity for multisensory plasticity. The present study examined whether the functions restored by the rehabilitation technique were limited to SC-mediated visuomotor detection and approach behaviors or, as suggested by recent studies, if they might include the ability to discriminate visual spatial patterns in the recovered hemifield. Animals were trained on a standard visual detection/localization task and a series of visual pattern discrimination tasks which required a judgement of whether a pair of brief (100ms) simultaneously-presented visual stimuli were the ‘same’ or ‘different’. The stimuli were either identical or systematically different along a chosen feature dimension (shape, size, direction of motion, or orientation). Pairs were presented within or across hemifields while animals fixated. They registered their decision by button press. Initially, animals could readily detect/approach visual stimuli and make pattern

discriminations well above chance on both sides of space. A large unilateral lesion of all contiguous areas of visual cortex rendered them hemianopic on one side of space. Several sessions of the multisensory exposure paradigm not only restored visual detection/localization in the contralesional hemifield, it restored the ability to discriminate visual patterns in the contralesional hemifield and across hemifields. Although discrimination ability was well above chance after rehabilitation, the animals' overall performance and sensitivity were impaired relative to pre-lesion levels. The results indicate that the visual processing restored by the cross-modal exposure paradigm extends well beyond the visually-guided behaviors commonly associated with midbrain circuits to include a broader set of visual discrimination capabilities more commonly associated with cortex.

**Disclosures: N.L. Bean:** None. **B.E. Stein:** None. **B.A. Rowland:** None.

**Poster**

**PSTR030. Cross-Modal Processing: Neural Circuitry and Development**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR030.21/BB14

**Topic:** D.08. Multisensory Integration

**Support:** MNESYS (PE0000006)

**Title:** Neural Mechanisms Underlying the Reversal of Hemianopia with Multisensory Training

**Authors:** C. CUPPINI[1], M. MONTI[1], ***B. E. STEIN**[2], B. ROWLAND[2];
[1]Univ. of Bologna, Bologna, Italy; [2]Wake Forest Univ. Sch. of Med., Winston Salem, NC

**Abstract:** Extensive damage to the visual cortex on one side of the brain often induces profound blindness in contralesional space (hemianopia). Recently, a non-invasive multisensory training paradigm has been shown to restore visual responsiveness within weeks. The paradigm consists of repeated pairings of auditory-visual stimuli in the blinded hemifield. Converging empirical evidence suggests that this training induces a functional reorganization within the remaining visual circuits that involve the midbrain superior colliculus (SC). The present study extends our computational model of this visual circuit (Cuppini et al., 2018) to explain the basis for this functional reorganization, as well as the return of visually guided behaviors and multisensory integrative abilities. In the model, lesions of visual cortex render neurons of association cortex (AES) and the multisensory (deep) layers of SC (SCd) unresponsive to visual cues. The return of visual function via multisensory training is explained by the operation of a normalizing Hebbian algorithm (Yu et al., 2018) within the residual visual circuit. In the model, elimination of afferents from visual cortex permits plasticity within the remaining circuit. During auditory-visual training the Hebbian algorithm strengthens the residual visual inputs, including a functional loop that involves SCd and association cortex. This restores visual responsiveness to neurons in AES and SCd, thereby supporting the restoration of visually guided behaviors to stimuli in the formerly blind hemifield. The model explains all empirical findings to date,

including the return of visual and multisensory processing, within a plausible unified neurocomputational framework.

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**Poster**

**PSTR030. Cross-Modal Processing: Neural Circuitry and Development**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR030.22/BB16

**Topic:** H.03. Decision Making

**Support:** 2022ZD0205000

**Title:** Contribution of macaque caudate nucleus to multisensory decision-making

**Authors: *Z. ZENG**[1,2], Y. GU[1,2];
[1]Inst. of Neuroscience, Chinese Acad. of Sci., Shanghai, China; [2]Univ. of Chinese Acad. of Sci., Beijing, China

**Abstract:** Combining noisy information originating from different sensory modalities to make more accurate and sensitive decisions is an efficient strategy adopted by many species, yet its underlying neural mechanisms remain unclear. Here we trained two macaque monkeys to utilize visual and vestibular evidence to perform a heading-discrimination task, during which we simultaneously recorded or manipulated neuronal activity in the caudate nucleus (CN). We found that the performance of both monkeys got significantly enhanced in the multisensory condition compared to unimodal condition. As to neural responses, a considerable proportion (more than 30%) of CN single neurons encoded both modality and choice-related signals. At the population level, CN activities represented upcoming choices but not sensory heading stimuli. Across time, temporal dynamics of CN activity were proportional to vestibular acceleration but visual speed, indicating that different temporal signals were employed for linear heading perception, which was also seen in other sensory-motor transformation areas including the parietal and frontal cortex. In the bimodal condition, moment-by-moment choice signals linearly weighted individual cue evidence according to their everchanging reliability. Finally, unilateral microstimulation (around 60 microamperes, 300Hz) applied to CN frequently biased monkeys' decisions about heading direction. In conclusion, CN plays an important role in multisensory heading perception.

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**Poster**

**PSTR031. Cerebellum: Cell Types and Circuit Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR031.01/BB17

**Topic:** E.02. Cerebellum

**Support:** The Nemours Foundation

**Title:** Isoform-specific function of Na,K-ATPase beta1-subunit in cerebellar granule cell function and cerebellum development

**Authors: M. RASHEED**[1,2], M. KHALIFE[1,3], A. CORT DONMEZ[1], K. SPERLE[1], Z. LI[1], E. TOKHTAEVA[4], N. W. LAMBRECHT[5], A. E. HERNAN[1,3], O. VAGIN[4], *S. A. LANGHANS[1]; [1]Nemours Children's Hlth. - Delaware, Wilmington, DE; [2]Biomed. Sci., [3]Psychological and Brain Sci., Univ. of Delaware, Newark, DE; [4]David Geffen Sch. of Med., UCLA, Los Angeles, CA; [5]Tibor Rubin VA Med. Ctr., Long Beach, CA

**Abstract:** Dysregulated catalytic activity of the Na,K-ATPase α-subunit has been implicated in neurological disorders associated with the cerebellum. In addition to its pumping function, the Na,K-ATPase exhibits pump-independent roles, wherein the α-subunit serves as a signaling scaffold, and the β-subunit isoforms, namely β1 and β2, function as cell adhesion molecules. Recent research has focused on unraveling the physiological significance of the pump-independent functions of Na,K-ATPase, particularly those attributed to its β-subunit. We aim to elucidate the specific role of the β1-isoform in the differentiation of cerebellar granule cells and cerebellar development.

We selectively deleted the β1-subunit in cerebellar granule cells in mice. The absence of β1 mRNA and protein in the cerebellum of homozygous knockout (KO) mice was confirmed by cerebellar genomic DNA analysis, immunoblotting, and β1 RNA in situ hybridization. Deletion of the β1-subunit in cerebellar granule cells resulted in complex neurological deficits. Heterozygous KO mice performed Barnes maze tests for learning and memory and social interaction and compared to their same-sex littermates exhibited deficiencies in these tasks. Homozygous KO mice, on the other hand, displayed symptoms consistent with cerebellar ataxia that worsened with age. Moreover, homozygous β1 KO mice had a shorter lifespan compared to heterozygous KO mice or control littermates. Interestingly, the phenotype observed in mice lacking the β1-subunit was markedly distinct from mice with deletion of the β2-subunit, suggesting that the β1-isoform plays a crucial and unique role in cerebellar granule cells and the development of the cerebellum.

To characterize the morphological changes in the cerebellum of adult mice lacking the β1-subunit, histology, immunohistochemistry, transmission electron microscopy, and magnetic resonance imaging (MRI) analyses were performed. Hematoxylin and eosin (H&E) staining did not reveal any discernible differences in cerebellar granule cells or the overall cerebellar architecture between the homozygous KO, heterozygous KO, and control littermate mice. Ex vivo, high-resolution MRI analysis of the cerebellum further confirmed the lack of significant structural differences between KO and control mice, although we observed a reduction in cerebellar volume in homozygous KOs. The reduction in volume was likely attributable to the smaller body size of the homozygous KO mice. Studies to identify molecular and electrophysiological changes underlying the morphological and functional deficiencies in mice with deletion of the β1-subunit in cerebellar granule cells are ongoing.

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**Poster**

**PSTR031. Cerebellum: Cell Types and Circuit Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR031.02/BB18

**Topic:** E.02. Cerebellum

**Support:** Original Technology Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT (No. 2021M3F3A2A01037811)
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**Title:** Input-dependent micromodules in the cerebellar granule cell layer: anatomical detection and computational modeling of the emergent process

**Authors:** I. JEON, Y. YAMAMOTO, H. PARK, K. TANAKA-YAMAMOTO, ***T. KIM**; Korea Inst. of Sci. and Technol. (KIST), Seoul, Korea, Republic of

**Abstract:** The cerebellar granule cell layer (GCL) refines inputs through mossy fiber (MF)-granule cell (GC) connections and relays them to Purkinje cells (PCs) via GC axons, parallel fibers (PFs). Since presumably identical GCs are densely packed, finding out governing rules for the GCL network seemed highly intricate. Considering the short dendrites of GCs, the connection probability of the MF-GC network was often assumed to be exclusively distance-dependent between them. Previously, we developed a technique for labeling a subgroup of GCs maturing at the same time, resulting in the band-shape of PF labeling in the molecular layer. By labeling two separate subgroups of GCs through our technique and ratiometric analysis compared with the network models representing possible cases, we showed that the MF-GC network has subtle heterogeneity that correlates with the developmental order of GCs; GCs that developed at the same time tended to connect to the same MF. We also showed that GC developmental order-dependent heterogeneity in MF-GC connection correlated with MF origins such as dorsal column nuclei (DoCN) or pontine nuclei (PN). Desynchronized time courses

between maturation of DoCN and PN MFs were detected, suggesting that the temporally matched development between MF and GC underlies the input-dependent heterogeneity. Because the subtle input-dependent heterogeneity could be interpreted as highly overlapping modules conveying different information, we developed a computational model that emulates the MF-GC network construction process. The model included the gradual migration and positioning of GCs and an origin-dependent MF maturation time course and allowed MFs and GCs to connect based on Euclidean distance and the coincidence of postulated spontaneous activities. Our model could regenerate the heterogeneity and parametrize its extent. We also implemented synaptic weight-dependent pruning of GC dendrites to mimic the known fact that immature GCs put out 2-3 times more dendrites than fully grown GCs. As the activities of MFs and GCs evolved synaptic weights by spike-timing dependent plasticity, the synapses with the lowest weights were pruned, and the overlapping modules that we found in the construction model emerged. For confirmation, we prepared several separated modules and induced overlaps between them, resulting in the regeneration of our prior model results. These imply that GCL may blend multimodal input information and provide a fused representation onto PCs. Further analysis of the resultant network parameters may reveal how GCL precisely orchestrates a variety of inputs for tasks where accuracy matters, such as smooth motor control.

**Disclosures: I. Jeon:** None. **Y. Yamamoto:** None. **H. Park:** None. **K. Tanaka-Yamamoto:** None. **T. Kim:** None.

**Poster**

**PSTR031. Cerebellum: Cell Types and Circuit Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR031.03/BB19

**Topic:** E.02. Cerebellum

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**Title:** Organization of Purkinje cell development by neuronal MEGF11 in cerebellar granule cells

**Authors: *S. JUN**[1], H. PARK[1], M. KIM[1,2], Y. YAMAMOTO[1], K. TANAKA-YAMAMOTO[1]; [1]Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [2]Div. of Bio-Medical Sci. and Technology, KIST Sch., Korea Univ. of Sci. and Technol. (UST), Seoul, Korea, Republic of

**Abstract:** Regularly organized cerebellar network structure is formed through dynamic developmental events during postnatal period, and developing granule cells (GCs) have been reported to coordinate this process. Whereas molecules involved in GC-mediated cerebellar

development have been identified, the regulatory mechanisms are not entirely understood. Given a general concept that developmental gene expression is tightly regulated based on necessity, it is reasonable to hypothesize that molecules in GCs exhibiting temporal variations in expression are highly relevant to a specific developmental process. Here we investigate the effects of the knockdown (KD) of multiple epidermal growth factor-like domains protein 11 (MEGF11), whose expression is substantially increased at the later developmental stages of GCs, on cerebellar postnatal development. We found that KD of MEGF11 in GCs resulted in several abnormal cerebellar structures, such as extensively ectopic Purkinje cell (PC) somas, disrupted GC migration, and abnormal excitatory synaptic formation, as well as in severely impaired motor functions, indicating that MEGF11 in GCs is required for the cerebellar development. The overexpression of MEGF11 in neurons restored most of abnormal cerebellar structures triggered by MEGF11 KD, confirming that the abnormal phenotypes arose from reduction of MEGF11 expression in GCs. Because MEGF11 KD at late stage of cerebellar development had only minor effects, there is a time window that MEGF11 works for proper network formation. We also detected abnormal synaptic transmission from parallel fibers (PFs), GC axons, to PCs by MEGF11-KD, which occurred before the emergence of any abnormal cerebellar structures we analyzed. This raises a possibility that the structural alterations were attributed to the functional changes in synaptic transmission. Indeed, blockade of this abnormal presynaptic release restored most of the cerebellar structures. Based on these results, we conclude that the impairment of cerebellar network formation caused by MEGF11-KD in GCs were mediated by abnormal PF synaptic transmission. In other words, MEGF11 in GCs promotes the establishment of cerebellar networks through regulating presynaptic release from PFs during postnatal developmental period.

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**Poster**

**PSTR031. Cerebellum: Cell Types and Circuit Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR031.04/BB20

**Topic:** E.02. Cerebellum

**Support:** NIH Grant: R01DA044761
NIH Grant: R01MH115604
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**Title:** Mechanisms of ethanol-induced motor attacks in Episodic Ataxia Type 2

**Authors: *J. TINDI**[1], H. SNELL[2], K. KHODAKHAH[3];
[1]Neurosci., [3]Dominick P. Purpura Dept. of Neurosci., [2]Albert Einstein Col. of Med., Bronx, NY

**Abstract:** Episodic ataxia type 2 (EA2) is a debilitating movement disorder characterized by periods of severe ataxia and dyskinesia (motor attacks) that are triggered by ethanol, caffeine, or stress. 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. Using the tottering mouse model of EA2, it has been shown that cerebellar Purkinje cell dysfunction is both necessary and sufficient for trigger-induced motor attacks. We have recently shown that stress can induce attacks through noradrenergic modulation of cerebellar Purkinje cell firing in a Casein Kinase 2 (CK2) and calmodulin dependent manner. We have also explored how ethanol triggers motor attacks in EA2. Like with stress, shRNA-mediated knockdown of CK2 in the cerebellum effectively prevented ethanol-induced motor attacks. However, in contrast to stress and caffeine-triggered attacks, ethanol did not increase phosphocalmodulin levels in Purkinje cells. Moreover, we found that ethanol did not directly affect CK2 kinase activity in vitro. Major targets of ethanol in the cerebellum are thought to be GABAergic and glutamatergic (NMDA-mediated) transmission. Low concentrations of ethanol can increase tonic inhibition in the cerebellar cortex that is mediated by δ subunit-containing GABA type A receptors (δ-$GABA_A$Rs). This increase requires the reduced activity of nitric oxide synthase in Golgi cells and an increase in GABA release onto cerebellar granule cells. We tested this possibility with the δ-$GABA_A$R-specific agonist THIP and found that it did not trigger attacks in tottering mice. Furthermore, modulation of nitric oxide synthase activity did not affect ethanol-induced attacks. Ethanol can also increase GABAergic inhibition by enhancing astrocytic production of GABA from ethanol metabolites. However, we found that metabolism of ethanol was not required for ethanol-induced attacks. Ethanol has also been shown to inhibit post-synaptic α6-subunit containing $GABA_A$Rs (α6-$GABA_A$Rs) on cerebellar granule cells. In line with this, attenuating α6-$GABA_A$R transmission in the cerebellum with furosemide was sufficient to trigger attacks in tottering mice. NMDA receptors (NMDARs) are also inhibited by low concentrations of ethanol, and we found that inhibition of NMDARs in the cerebellum is sufficient to trigger motor attacks. Given these findings, it would be prudent to explore whether inhibition of α6-$GABA_A$Rs or NMDARs requires CK2 activation and may be the mechanism by which ethanol triggers attacks in the tottering mice.

**Disclosures:** **J. Tindi:** None. **H. Snell:** None. **K. Khodakhah:** None.

**Poster**

**PSTR031. Cerebellum: Cell Types and Circuit Physiology**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR031.05/BB21

**Topic:** E.02. Cerebellum

**Support:** NIH Grant DC016905
Hearing Health Foundation
National Ataxia Foundation

**Title:** Feed-forward networks of unipolar brush cells extend and diversify sensory signaling in the cerebellum

**Authors: *H. N. HARIANI**, A. B. ALGSTAM, C. T. CANDLER, I. F. WITTEVEEN, J. K. SIDHU, T. S. BALMER;
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**Abstract:** Sensory signals are processed by the cerebellum to coordinate movements across time scales from milliseconds to seconds. Numerous cerebellar functions are thought to require the maintenance of a sensory representation that extends beyond the input signal. How the cerebellar circuit extends brief sensory signals for long durations is not well understood. Granule cells constitute the main cell type that receives sensory input, but they do not prolong the signal and are thus unlikely to maintain a sensory representation for much longer than their inputs. Another cell type that could prolong signals is the unipolar brush cell (UBC). UBCs are excitatory interneurons that receive sensory input that they extend and modify before projecting to granule cells. UBCs can be divided into ON and OFF subtypes that transform sensory input into prolonged increases or decreases in firing. Further extension and diversification of the input signal could be produced by UBCs that project to one another. Although there is evidence that UBCs target one another, it is unclear whether ON and OFF subtypes form distinct parallel pathways or if the ON and OFF subtypes innervate one another. Here we examine feed-forward networks of UBCs and explore how they could transform spiking patterns. We characterized two transgenic mouse lines electrophysiologically and immunohistochemically to confirm that they label ON and OFF UBC subtypes, and then crossed them together, revealing that ON and OFF UBCs innervate one another. A Brainbow reporter was used to label UBCs of the same ON or OFF subtype with different fluorescent proteins, which showed that UBCs innervate their own subtypes as well. An optogenetic approach confirmed that ON UBCs synapse directly onto other ON UBCs. Finally, we develop computational models that predict that these feed-forward networks of UBCs extend the length of bursts or pauses and introduce delays—transformations that may be necessary for cerebellar functions from modulation of eye movements to adaptive learning across time scales.

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**Poster**

**PSTR031. Cerebellum: Cell Types and Circuit Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

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**Topic:** E.02. Cerebellum

**Support:** European Union’s Horizon 2020 Framework Program for Research and Innovation under the Specific Grant Agreement No. 945539 (Human Brain Project SGA3)

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**Title:** Apical-to-basal dendritic communication drives STDP on the theta-band at cerebellar Golgi cell-mossy fiber synapses

**Authors: *E. PALI**[1], T. SORBO[1], F. PRESTORI[1], E. D'ANGELO[1,2];
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**Abstract:** Interneurons are key to guide information processing in neuronal networks. At the cerebellar input stage, Golgi cells (GoCs) are known to integrate parallel fiber (pf) and mossy fiber (mf) synaptic inputs on their apical and basal dendrites. However, the functional relevance of this input segregation has not been revealed yet. Recently, a detailed computational model (Masoli et al., PLoS Comput Biol. 2020 Dec 30;16(12):e1007937) predicted that GoC apical dendrites control spike back-propagation toward basal dendrites, eventually regulating NMDA receptor (NMDAR) channel unblock at mf-GoC synapses. The NMDARs would thus operate as coincidence detectors of mf and pf activity and drive spike-timing dependent plasticity (STDP) depending on the relative phase of mf and pf activity. Here, we investigated experimentally whether mf-GoC STDP would actually occur following patterned mf and pf stimulation. We performed whole-cell patch-clamp recordings (n=97 GoCs total) in acute coronal slices of cerebellum in GlyT2 transgenic mice by repeating (at 4 Hz for 60 times) mf-pf stimulus pairs with specific phase differences (±10, ±25, ±50, ±100 ms). Mf-GoC plasticity showed a peculiar temporal order-dependence, with LTP (long-term potentiation) or LTD (long-term depression) occurring when mf anticipated or followed pf stimulation, respectively, configuring typical STDP. The phase and timing between mf and pf inputs were the two critical determinants of the direction and degree of mf-GoC plasticity. In the presence of NMDAR inhibitors (100 μM APV and 50 μM 7-Cl Kyn), STDP was abolished. These experiments fully confirm model predictions that mf-GoC STDP is driven by apical-to-basal dendritic communication under NMDAR control. In addition, we investigated the eligible frequency window for mf-GoC STDP induction by varying the repetition interval of stimulus pairing. We found that STDP was optimally induced with 4 Hz pairing but vanished when pairing mf and pf inputs at 1 and 10 Hz. This suggests that mf-GoC STDP is instrumental to confine learning in the theta-band (4-8 Hz), at which granule cells and GoCs show oscillations and resonance. We can therefore set out the novel hypothesis that GoCs, thanks to their double dendritic arborization (that allows pf and mf input combinations), the specific expression of ionic channels (that allow spike backpropagation), and synaptic NMDA receptors (that allow voltage-dependent Ca-entry in the basal dendrites), operate as *circuit coincidence detectors* between the granular and molecular layer. This detector is tuned on the theta-band, which provides a preferential frequency band for cerebellar computation and learning.

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**Poster**

**PSTR031. Cerebellum: Cell Types and Circuit Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR031.07/BB23

**Topic:** E.02. Cerebellum

**Support:** OIST Graduate University

**Title:** Multiplexed coding in a heterogenous ion channel density branch-specific Purkinje cell model

**Authors:** G. CIRTALA, ***E. DE SCHUTTER**;
Okinawa Inst. of Sci. and Technol., Onna-Son, Japan

**Abstract:** Purkinje cell (PCs) are the most prominent cell types in the cerebellum and represent the only output of the cerebellar cortex. Their dendritic trees are characterized by complex and extensive branching, offering PCs the ability to receive more inputs than any other cell type in the brain. PCs receive sensorimotor information through parallel fiber (PF) and encode it with immense accuracy. Elucidating how PCs encode the information provoked a lot of debate over the last years, with some authors suggesting that PCs encode the PF via linear encoding, while others observing a burst-pause coding response. The emergent theory known as multiplexed coding, unifies these two different observations and suggests that the brain is highly optimized to process information and therefore, uses a combination of linear and burst-pause coding. Evidence of multiplexed coding was found in the human basal ganglia, somatosensory cortex, in the basal forebrain, and was recently captured in the cerebellum through a computational PC model by Zang and De Schutter (2021). When simulating clustered PF input, the authors discovered that most dendritic branches of the PC linearly integrate PF, while few others generate localized all-or-none dendritic spikes. Based on this model, our research explores the multiplexed coding in PCs in response to a clustered PF input and shows how changing the biophysical properties of the cell, results in a shift of the coding strategy. We developed the first heterogenous ion channel density PC model, in which each branch of the PC is characterized by its own ion channel conductance density and we simulated PF input on each branch of the PC. We recorded the amplitude response with respect to the activated PF synapses, and we determined whether this response is bimodal or linear. We show that by altering various ion channel conductance densities such as P type Calcium channel (CaP), potassium Kv4 channel and small conductance calcium activated potassium (SK2) channel, we can shift the encoding strategy from linear to bimodal step-plateau and vice-versa, therefore obtaining a uniform mechanism throughout the cell. We determined the minimum number of activated PF required to generate the bimodal step-plateau response in each branch and we discuss the morphological factors that might contribute to this variation. We show how the dendritic spikes initiate and propagate within each activated branch and we investigate the effect at the soma by quantifying the somatic pauses. Lastly, we discuss co-activation of different branches, its effect on the bimodal response and its minimum PF threshold, and we show how the somatic pauses compare to the single activated branches.

**Disclosures:** **G. Cirtala:** None. **E. De Schutter:** None.

**Poster**

**PSTR031. Cerebellum: Cell Types and Circuit Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR031.08/BB24

**Topic:** E.02. Cerebellum

**Support:** SFB 1451

**Title:** Endocytic adaptor AP-2 maintains Purkinje cell function by regulating the balance of cerebellar parallel and climbing fiber synapses

**Authors: *M. TOLVE**[1,2], J. TUTAS[2], A. GALVÃO[3], F. LIEBSCH[4], E. ÖZER-YILDIZ[2], E. KOLETSOU[2], M. OVERHOFF[1,2], M. KROHN[2], S. CAMBLOR-PERUJO[2], G. SCHWARZ[4], G. GATTO[3], N. L. KONONENKO[1,2];
[1]Ctr. for Physiol. and Pathophysiology, Fac. of Med. and Univ. Hosp. Cologne, Univ. of Cologne, Cologne, Germany; [2]Cologne Excellence Cluster Cell. Stress Response in Aging-Associated Dis. (CECAD), Univ. of Cologne, Cologne, Germany, Cologne, Germany; [3]Neurol. Department, Univ. Hosp. of Cologne, Cologne, 50937, Germany., Cologne, Germany; [4]Inst. of Biochemistry, Dept. of Chemistry, Univ. of Cologne, Cologne 50674, Germany., Cologne, Germany

**Abstract:** The selective loss of cerebellar Purkinje cells (PCs) is a common hallmark of several neurodegenerative movement disorders. The mechanism underlying their selective vulnerability has not been yet identified. Here we show that endocytic adaptor AP-2, previously described to be required for functional autophagosome trafficking in neurons, is essential to maintain the survival of PCs. By combining mouse genetics, proteomics, adeno-associated viruses-based tracing, 3D reconstructions, ex vivo-calcium imaging and behavioral approaches we reveal that mice lacking the μ subunit of the AP-2 complex in cerebellar PCs develop severe gait abnormalities accompanied by PCs progressive degeneration. Importantly, synaptic inputs dysfunction, characterized by a dominance of parallel fiber (PF) over climbing fiber (CF) synapses precedes the PCs loss. We identified Delphilin as a novel AP-2 binding partner in the cerebellum. Delphilin is a postsynaptic scaffolding protein selectively expressed at the parallel fiber-PCs synapse. Delphilin interacts with the glutamate δ2 receptor (GRID2) and is proposed to control the PC functions by linking GRID2 to the actin cytoskeleton and signaling molecules. GRID2 is essential for cerebellar long-term depression, motor learning and PF synapse formation and its loss in humans causes spinocerebellar ataxia type 18. AP-2-deficient PCs reveal loss of synaptic Delphilin and accumulation of GRID2 to distal dendrites, a phenotype which results in PF/CF misbalance in the cerebellum of conditional AP-2 KO mice. Moreover, proteomics data obtained from the cerebellum of these mice show upregulation of proteins involved in processes such as synaptic pruning and downregulation of proteins related to long term depression and spinocerebellar ataxia. Interestingly, overrepresentation of PF leads to PC hyperexcitation that can be rescued by facilitating synaptic glutamate clearance. Our data suggest that AP2 prevents

motor gait dysfunction by dendritic levels of GRID2 in PCs, which is required to maintain synaptic connectivity in the cerebellum.

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**Poster**

**PSTR031. Cerebellum: Cell Types and Circuit Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR031.09/BB25

**Topic:** E.02. Cerebellum

**Support:** NIH Grant T32HL007446
NIH Grant NS123933

**Title:** Parallel fiber metaplasticity mediated by cannabinoid type 1 receptors

**Authors: *C. HUNLEY**[1], S. MITRA[2], J. PUGH[3];
[1]UT Hlth. San Antonio Physiol. and Pharmacol. Div., San Antonio, TX; [2]Univ. of Texas Hlth. Sci. Ctr. San Ant, SAN ANTONIO, TX; [3]UTHSCSA, San Antonio, TX

**Abstract:** The acquisition and storage of learned responses in the cerebellar circuit are primarily mediated by long-term changes in synaptic strength at parallel fiber (PF)-Purkinje cell (PC) synapses. The activity patterns and cellular mechanisms required for long-term potentiation (LTP) or depression (LTD) at these synapses have been studied in detail. However, both behavioral experiments and computational models suggest that mechanisms must also exist to regulate the level of plasticity possible at individual synapses for proper response acquisition and retention. For example, in early stages of learning, it is advantageous for PF synapses to be highly plastic, thus allowing for rapid and large changes in synaptic strength, whereas late in learning, it is beneficial for synapses to have relatively stable synaptic strengths, which allow for fine-tuning and retention of learning. However, cellular mechanisms mediating metaplasticity in the cerebellum are still unclear. Elucidation of mechanisms that mediate metaplasticity is fundamental for an accurate understanding of how learned responses are acquired and stored in the cerebellar circuit. Previous studies have shown that pharmacological or genetic ablation of CB1Rs prevents LTP and LTD induction at PF synapses and impairs cerebellar learning. Further we have shown that CB1R expression is a plastic property of PF synapses, suggesting changes in CB1R expression may regulate PF plasticity. To test this hypothesis, we used Depolarization Induced Suppression of Excitation (DSE) to measure CB1R activity. Our results show that DSE is highly variable across PF synapses. Further, we found a strong correlation between CB1R activity (measured by DSE) and the magnitude of subsequent LTD induced at the same synapses. Likewise, we found that partial inhibition of CB1Rs by subsaturating AM-251 (10-100nm) inhibit DSE and LTD induction to a similar extent. Together, these data suggest that differences

in presynaptic CB1R activity are a critical determinant of LTP induction at PF synapses. Finally, we measured DSE amplitude before and after LTD induction at the same synapses; we found that DSE is significantly reduced following LTP induction, suggesting a down-regulation of CB1R activity. Interestingly, the change in DSE following LTD induction is highly correlated (r=0.92) with the magnitude of LTD. These data suggest CB1R activity is reduced following synaptic plasticity, limiting further plasticity at the same synapses. Our data indicates that presynaptic PF CB1Rs may be key to balancing acquisition and retention of functional memory by managing transitions between levels of plasticity.

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**Poster**

**PSTR031. Cerebellum: Cell Types and Circuit Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR031.10/CC1

**Topic:** E.02. Cerebellum

**Support:** NIH Grant 5R01DA044761-06

**Title:** Locus Coeruleus noradrenergic-dependent modulation of spontaneous and evoked activity in cerebellar Purkinje cells

**Authors: *L. SPAETH**, J. VERA, K. KHODAKHAH;
Dominick P. Purpura Dept. of Neurosci., Albert Einstein Col. of Med., Bronx, NY

**Abstract:** The cerebellum is involved in motor coordination, learning, and execution. In normal conditions, it enables the animal to perform smooth and accurate movements by predicting and steering the outcome of ongoing actions. Yet, numerous studies show that, in stressful situations, proper movement execution can be impaired, thus pointing to a potential effect of stress on cerebellar function. However, mechanisms underlying stress-induced deficits in motor accuracy remain poorly understood. In the brain, acute stress primarily activates the noradrenergic system, particularly the Locus Coeruleus (LC). The LC releases norepinephrine (NE), a neuromodulator known to regulate neuronal excitability and synaptic gain to promote vigilance and optimal performance. Recent evidence from our laboratory showed that NE signaling in the cerebellum is responsible for the onset of stress-induced motor attacks in a mouse model of cerebellar ataxia, through direct modulation of cerebellar Purkinje cells (PCs). The goal of this project is to understand the LC NE-dependent modulation of sensorimotor integration by PCs. PCs are the main computational unit, and the sole output of the cerebellar cortex. They are spontaneously active and fire regularly, allowing them to encode somatosensory information conveyed by granule cells and molecular layer interneurons with high precision. We found that bath-application of NE in acute cerebellar slices of wild type mice (1) reduced the regularity of spontaneous firing in PCs and (2) either potentiated or reduced their responses to granule cell inputs. Using Slc6a2-Cre (NET-Cre) mice to selectively explore and manipulate the LC-NE

projections, we found that LC sends NE fibers to the entire cerebellum, suggesting that it has a large potential for exertion of its modulatory effects throughout the cerebellum. Finally, specific expression of ChR2 in LC-NE neurons showed that optogenetic release of endogenous NE from LC projections was sufficient to (1) slow down and (2) reduce the regularity of spontaneous firing in cerebellar PCs. Our experiments provide an approach for investigation of how stress influences the neuronal computations and the physiology of the cerebellum.

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**Poster**

**PSTR031. Cerebellum: Cell Types and Circuit Physiology**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR031.11/CC2

**Topic:** E.02. Cerebellum

**Support:** Deutsche Forschungsgemeinschaft (SFB 870)
Max-Planck-School of Cognition
Hertie-Stiftung

**Title:** In vivo single-synapse glutamate imaging in cerebellar Purkinje cells of behaving mice

**Authors:** ***M. KLOOS**[1], Y. CHEN[1], B. SONG[1], Y. YAROM[2,3], I. NELKEN[2,3], A. KONNERTH[1];
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**Abstract:** A core function of the cerebellum is the integration of sensory and motor information in view of an optimal planning and control of movement. The final cerebellar stage of synaptic signal integration are the Purkinje cells (PCs), each of them integrating many thousands synaptic inputs from afferent excitatory parallel fibers (PF), originating from mossy fiber input-receiving granule cells, and climbing fiber (CF) synapses, originating from inferior olive neurons, as well as inputs from a diverse set of inhibitory synapses. A recent study reported a bi-directional cerebellar control of movement in head-fixed mice running on a wheel (Lanore et al, 2021). By using axonal calcium imaging for the monitoring of PF activity, those authors found that distinct sets of PFs were active during the active state (AS), when the animals were running, versus quiet wakefulness (QW), when the mice were resting on the wheel.
For gaining an understanding of the downstream processing of these opposite synaptic signals in PCs, we devised an approach for functional two-photon single-synapse imaging in head-fixed, behaving mice. For this purpose, we electroporated plasmids of either a genetically-encoded calcium indicator, such as GCaMP8m, or of the genetically-encoded glutamate indicator iGluSnFR3 (Agarwal et al, 2023) into individual PCs. In both cases, the corresponding sensor was successfully expressed a few days later, allowing calcium and glutamate imaging in spiny dendrites of PCs, respectively, for many consecutive recording sessions during the following

days and weeks. Our results demonstrate the feasibility of in vivo functional single synapse visualization and separation of PF and CF inputs, using both calcium or glutamate imaging. Particularly insightful for the analysis of the integration of afferent sensorimotor synaptic signals was glutamate imaging, as it offers the possibility to measure PF inputs at single event resolution. In individual PCs we identified two highly distinct groups of PF synapses. One group was highly active exclusively during the AS, while the second group was active, displaying a characteristic burst pattern, exclusively during QW.
Thus, by using two-photon glutamate imaging of single synapses in awake, head-fixed mice running on a wheel, we demonstrate that the individual PCs can integrate apparently opposing afferent sensorimotor input signals to form output signals, consisting of simple spike activity, that are conform with the behavioral requirements.

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**Poster**

**PSTR031. Cerebellum: Cell Types and Circuit Physiology**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR031.12/CC3

**Topic:** E.02. Cerebellum

**Support:** Department of Atomic Energy, Government of India
DBT-Wellcome Trust Senior Fellowship

**Title:** Calcium Dynamics Driving Spontaneous Activity in Zebrafish Purkinje Cell

**Authors: *M. JADHAV**, V. THIRUMALAI;
Natl. Ctr. for Biol. Sci., Tata Inst. of Fundamental Res., Bengaluru, India

**Abstract:** Purkinje cells act as a central hub of the cerebellum, receiving numerous inputs, and combining them to fine-tune movement. The cells also spontaneously fire simple spikes either regularly (Tonic) or in bursts. An understanding of their biophysics and intrinsic properties will help elucidate how they integrate various signals and contribute to the cerebellar function. Zebrafish provide an excellent system where physiological recordings can be easily done in an awake and behaving animal. However, the physiology and biophysics of their cells remain unclear. Larval zebrafish Purkinje cells show large calcium currents. Studies in mammalian systems have also pointed toward the role of dendritic calcium spikes in modulating bursting, firing frequency, and bistability.
We, therefore, decided to look at the role of calcium channels in driving zebrafish Purkinje cell activity We used 6- 8 days-old larvae for all our experiments. We performed in vivo whole-cell patch clamp electrophysiology to identify calcium channel subtypes and their effects on Purkinje cell spontaneous activity.
By performing voltage clamp experiments with pharmacological agents, we found that the

calcium current is mainly contributed by L and T-type voltage-gated calcium channels. We then observed the effect of various channel antagonists on the spontaneous activity of these cells in the current clamp mode. We found that blocking L-type channels caused simple spike frequency to decrease in the tonic mode. We also observed a broadening of spikes with an increase in decay time, implicating these channels in the repolarization mechanism, presumably via calcium-dependent potassium channels. Interestingly, blocking SK channels mimicked the effects of the L-type block.
We further confirmed this with a reduced, biophysical model of tonically firing cells. The output of the model was validated with our in vivo data. The model also showed an L-type channel-driven activation of SK channels helps maintain a pool of sodium channels to drive simple spikes.
Together, these results point show that L-type calcium channels mediated SK channel activation is central to maintaining tonic activity in zebrafish Purkinje cells.

**Disclosures: M. Jadhav:** None. **V. Thirumalai:** None.

**Poster**

**PSTR031. Cerebellum: Cell Types and Circuit Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR031.13/CC4

**Topic:** E.02. Cerebellum

**Support:** 1R37NS128416

**Title:** Temporal coordination of spikes in the cerebellum reveals connectivity patterns of Molecular layer interneurons and Purkinje Cells during saccades

**Authors: *M. FAKHARIAN**[1], A. SHOUP[1], J. ZANG[1], P. HAGE[3], J. PI[2], R. SHADMEHR[4]; [1]Johns Hopkins Univ., Baltimore, MD; [2]Johns Hopkins Univ., Johns Hopkins Univ., Ellicott City, MD; [3]Johns Hopkins Univ. Sch. of Med., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [4]Johns Hopkins Univ., Johns Hopkins Univ. Dept. of Biomed. Engin., Baltimore, MD

**Abstract:** During movements such as saccades and reaching, Purkinje cells (P-cells), the output cells of the cerebellar cortex, not only modulate their firing rates, but also temporally synchronize their simple spikes. How does this temporal coordination arise? We hypothesized that the molecular layer interneurons (MLIs), such as basket and stellate cells, precisely time their activities in order to organize the simple spikes of P-cells across a population, synchronizing them during specific phases of a movement.
We recorded from the oculomotor vermis using high-density silicon probes in marmosets while they performed saccadic eye movements. These probes allowed us to simultaneously record from multiple layers of the vermis, enabling us to not only identify different putative cell types, but also their spike interactions. P-Cells were definitively identified because of a suppression of the simple spikes via complex spikes. However, the identification of other cell types was more

challenging. To distinguish cell types, we examined their electrophysiological signatures, including spike waveforms, relative positions on the electrode compared to P-cells, and auto- and cross-correlograms. The molecular layer was identified by observing negative, low-frequency shaped complex spikes, the absence of stereotypic triphasic mossy fibers, the presence of sparse and small interneurons near P-Cells (MLIs), and the inhibition of P-cells by these cells on a millisecond time-scale.
Next, we investigated the interaction between putative MLIs and P-cells during movement. We utilized linear and non-linear statistical methods to measure the distance between the joint probability of spiking in two neurons and the expected probability in statistically independent neurons. These results provided a time-dependent measure of temporal coordination among the neurons' states. By employing this approach, we quantified how the cell-cell interactions changed during a movement, irrespective of the firing rate. To dissociate the effect of firing rate on temporal coordination, we used trials shuffling as a control.
We found that during saccades, P-cells synchronized their simple spikes with other P-cells, and MLIs synchronized their spikes with other MLIs. This synchronization was task related, direction-dependent, and much greater than during baseline conditions. Critically, MLIs exhibited stronger inhibition of P-cells during saccades than during baseline. Thus, it appears that during saccades, MLIs and P-cells not only synchronize their spikes with each other, but that MLIs play a role in promoting synchronization of P-cell simple spikes.

**Disclosures:** **M. Fakharian:** None. **A. Shoup:** None. **J. Zang:** None. **P. Hage:** None. **J. Pi:** None. **R. Shadmehr:** None.

**Poster**

**PSTR031. Cerebellum: Cell Types and Circuit Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR031.14/CC5

**Topic:** E.02. Cerebellum

**Support:** NIH Grant NS112518

**Title:** Loss of inhibition to purkinje cells increases activity in cerebellar nucleus neurons

**Authors: *M. SMITH**, E. KROOK-MAGNUSON;
Univ. of Minnesota, Minneapolis, MN

**Abstract:** Selectively knocking out the GABAAα1 subunit of GABA receptors in Purkinje cells produces a phenotypic tremor reminiscent of that seen in essential tremor patients. Purkinje cells only express the alpha one subunit, and do not upregulate any other alpha isoforms when alpha 1 is knocked out. Therefore, loss of the GABAAα1 subunit from PCs results in a complete loss of GABAA mediated inhibition to Purkinje cells. As such, animals with a loss of GABAAα1 selectively in Purkinje cells provide a means to examine the role of precisely timed inhibition to Purkinje cells in cerebellar physiology, including activity in the downstream cerebellar nuclei

(DCN). Purkinje cells provide inhibitory connections to the DCN, including the medial, fastigial nucleus (FN). We examined how activity in the FN is affected by the pathophysiology of Purkinje cells in the GABAAα1 knock out (KO) model. Using broad viral targeting of the FN to express RCaMP, we performed calcium imaging with fiber photometry in freely moving animals during open field testing. While DCN neurons are inhibited by asynchronous firing of Purkinje cells, they can also show rebound firing following synchronized inputs. We hypothesize that loss of GABAAergic inhibition to Purkinje cells will increase their synchronization, and thereby increase activity in downstream DCN neurons (despite Purkinje cells being inhibitory neurons). We predicted that this would result in an increase in both the amplitude and frequency of calcium events recorded in the FN in KO animals compared to wild-types (WT). We found that KO mice (n=6) had a significantly increased amplitude of events in the FN when compared to WT littermates (n=4) (average z-score amplitude, WT: 3.47±0.25, KO: 4.76±0.45; p = 0.043, Mann-Whitney), and there is a trending increase in frequency (WT: 0.22±0.01 Hz, KO: 0.44±0.07 Hz; p = 0.11, Mann-Whitney). This shows that loss of inhibition to Purkinje cells can, somewhat counterintuitively, increase activity levels in the downstream DCN. Ongoing work examines how the behavioral state of the animal, including locomotion, may impact activity in the DCN and the impact of loss of inhibition to Purkinje cells on the activity in the DCN, the impact on downstream structures, including the thalamus, and how this pathophysiology may relate to behavioral phenotypes.

**Disclosures: M. Smith:** None. **E. Krook-Magnuson:** None.

**Poster**

**PSTR031. Cerebellum: Cell Types and Circuit Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR031.15/CC6

**Topic:** E.02. Cerebellum

**Support:** Wellcome Trust-DBT India Alliance Intermediate and Senior fellowships
Department of Biotechnology
Science and Engineering Research Board, Department of Science and Technology
Department of Atomic Energy
NCBS-TIFR graduate student fellowship

**Title:** Highly synchronized inhibition from Purkinje cells entrains cerebellar output in zebrafish

**Authors: *V. AGARWAL**, S. NARAYANAN, S. CHINTA, V. THIRUMALAI;
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**Abstract:** The cerebellum is a brain region involved in motor control and coordination. Cerebellar Purkinje cells (PCs) integrate inputs from two major excitatory pathways: parallel fibers and climbing fibers. PCs provide convergent inhibitory inputs to cerebellar output neurons

in the deep cerebellar nuclei (DCN) in mammals and eurydendroid cells (ECs) in zebrafish. It is known that both PCs and DCN (Thach,1978; Heck et al.,2007) as well as ECs (our results and Harmon et al.,2020) show elevation in firing either coincident with or around the onset of movements. These results demonstrate that PCs and ECs do not share an inverse average firing rate relationship. Therefore, we hypothesized that PCs modulate the activity of DCN/ECs over millisecond time scales, i.e. EC spikes will be time-locked to PC inter-spike intervals due to relief from inhibition. In this study we tested whether this is true using a combination of optogenetics and electrophysiology in larval zebrafish. In transgenic larval zebrafish expressing channelrhodopsin specifically in PCs, we were able to elicit reliable responses to high frequency light pulses. We were able to modulate the extent of synchrony in PC population from very low to near perfect estimated synchrony by varying the intensity of light pulses. Next, we recorded the activity of ECs while precisely regulating the synchrony of PCs. We found that even though PC firing rate consistently more than doubled during stimulation, there was no consistent change in EC activity during the same period. EC spike probability dips to a minimum around 10ms after the PC stimulation is over. However, this modulation of EC activity does not happen when PCs are asynchronously activated. These results suggest that spike timing synchrony is a plausible mechanism to modulate cerebellar output.

**Disclosures: V. Agarwal:** None. **S. Narayanan:** None. **S. Chinta:** None. **V. Thirumalai:** None.

**Poster**

**PSTR031. Cerebellum: Cell Types and Circuit Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR031.16/CC7

**Topic:** E.02. Cerebellum

**Support:** NSFC Grant No. 82271269

**Title:** Disturbed outputs from the glutamatergic neurons in deep cerebellar nuclei trigger the dyskinetic movements

**Authors: *X.-M. WU**[1,2,3], B. LU[1,2], Z.-Q. XIONG[1,2,3];
[1]Inst. of Neuroscience, Chinese Acad. of Sci., Shanghai, China; [2]Univ. of Chinese Acad. of Sci., Beijing, China; [3]Sch. of Life Sci. and Technology, ShanghaiTech Univ., Shanghai, China

**Abstract:** Dystonia is a movement disorder charactered by involuntary sustained or intermittent muscle contractions, which results in repetitive twisting movements or abnormal postures. While the deep cerebellar nuclei (DCN) have been implicated in dystonia, the exact roles of distinct neuronal subpopulations in the DCN for controlling these dyskinetic behaviors are unknown. Here we used the *Prrt2*-deficient mice, an animal model of Paroxysmal Kinesigenic Dyskinesia (PKD), to dissect the functions of DCN glutamatergic, GABAergic and glycinergic neurons in dystonia attacks. We used cell-type targeting, recording, manipulating and ablating strategies to

identify the critical groups of DCN neurons that mediating the featured dyskinetic movements. Calcium signals recording with fiber photometry revealed that DCN glutamatergic, glycinergic, GABAergic inferior olive (IO) projecting and GABAergic non-IO projecting neurons were all sustainably activated during dystonic movements in *Prrt2*-deficient mice (n = 14-20 trials for each group from 3-5 mice). Optogenetically activating DCN glutamatergic and GABAergic non-IO-projecting neurons rather than glycinergic and GABAergic IO projecting neurons induced dystonia-like behaviors (n = 16 trials for each group from 4 mice). Ablation of DCN glutamatergic neurons eliminated aberrant outputs of the cerebellum to the ventral thalamus and alleviated cerebellum-originated dyskinetic movements in *Prrt2*-deficient mice (n = 5 mice). These results suggest that aberrant activation of DCN glutamatergic neurons underlies the neuropathological mechanisms of paroxysmal dyskinesia.

**Disclosures: X. Wu:** None. **B. Lu:** None. **Z. Xiong:** None.

**Poster**

**PSTR032. Movement Selection and Execution of Skilled Movements**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR032.01/CC8

**Topic:** E.04. Voluntary Movements

**Support:** NIH Grant NS109315
BSF Grant 2021248
NVIDIA

**Title:** Non-dominance as coarse-graining at the level of movement trajectory shape representation

**Authors: *A. ARAC**[1], N. Y. H. JEONG LEE[1], I. DRYDEN[2], J. W. KRAKAUER[3];
[1]Neurol., UCLA, Los Angeles, CA; [2]Mathematics and Statistics, Florida Intl. Univ., Miami, FL; [3]Johns Hopkins Univ., Johns Hopkins Univ., Baltimore, MD

**Abstract:** Handedness is a human-specific feature of motor control, characterized by higher quality of skilled movements on the dominant side. According to the dynamic-dominance hypothesis, the key factor that results in the better performance on the dominant side is the control of limb dynamics [1]. We hypothesized that handedness is not a motor execution problem *per se* but a trajectory shape-selection problem. For example, when writing a letter “A” with your non-dominant hand it looks wrong, but it is executed just as well as when you copy the “bad” A with your dominant side. On the non-dominant side, there seems to be a mismatch between what you want the A to look like and how it comes out. This is not that different to being bad at drawing, which is clearly not a low-level motor control problem but more a problem of resolution - you want that tree branch to come out in all its detail, but a crude stick comes out instead. This can be considered a form of involuntary coarse-graining - details are smoothed out that you don’t want to smooth out. To test this “shape-selection” idea, we first devised a novel

experimental setup of 3D center-out reaching task and measured 3D kinematics with a marker-less method. We performed three experiments on young, healthy, right-handed subjects. In the first experiment, the subjects reached to five different targets. In the second experiment, subjects performed the same task but with a 5 lbs weight on their wrists, which altered limb dynamics. In the third experiment, we “elongated” the subjects’ forearms by attaching a stick, mimicking tool use. We compared the 3D end-effector trajectory shapes using statistical shape analysis. Our results showed that in the first experiment, the non-dominant side showed higher variance but no trajectory shape differences. In the second experiment, the variance in both groups increased significantly but there was no effect on shape on either side and no difference between sides. In the third experiment, the variance again increased significantly on both sides but did so more on the non-dominant side. Most notably, there was also a significant shape change between the stick and no-stick conditions as well as between right and left of the stick reaches. We conclude that non-dominance is brought out when the shape or geometry of a movement is stressed, which is the case with tools. The difference may be due to a kind of information bottleneck, where there is a cost to having fine-grained resolution that maps between a target goal and the number of command options available to achieve it. Practice, which has a large opportunity cost, may overcome this. References:1. Sainburg, R. Exp Brain Res (2002) 142:241-258

**Disclosures: A. Arac:** None. **N.Y.H. Jeong Lee:** None. **I. Dryden:** None. **J.W. Krakauer:** None.

**Poster**

**PSTR032. Movement Selection and Execution of Skilled Movements**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR032.02/CC9

**Topic:** E.04. Voluntary Movements

**Support:** Discovery Grant, Natural Sciences and Engineering Research Council of Canada

**Title:** What's touch got to do with musicians' motor performance? The role of expertise in tactile perception during movement planning

**Authors: *J. TOM**, J. X. MANZONE, J. L. CHEN;
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**Abstract:** According to the ‘Touch Paradox’, despite the fact that tactile perception is crucial to motor performance, tactile perception is frequently suppressed in movement contexts. Peripheral signals block tactile perception during movement execution. Central signals block tactile perception during movement planning when upcoming tactile inputs are predictable. The aim of our study is to investigate the influence of expertise on tactile suppression during the planning of an expert motor task (i.e., a piano key press), comparing expert pianists to musically untrained individuals. We hypothesized that expert pianists will show more tactile suppression in planning

a piano key press than musically untrained individuals. This is the first-known study to test whether tactile suppression during movement planning is expertise-dependent.
We plan to study 24 right-handed participants (18-60 y): 12 expert pianists (Expert) and 12 musically untrained individuals (Untrained). We have currently tested 5 Experts (2 male, 3 female; mean: 40.8 y) and 5 Untrained (3 male, 2 female; mean: 28.8 y).
We tested tactile perception by presenting weak electrical currents from a Digitimer DS-4 stimulator to the skin under 3 conditions of a piano key press: 1) baseline (i.e., at rest); 2) planning (i.e., 300 ms prior to key press); 3) execution (i.e., synchronous with key press). The perceptual threshold was defined as the stimulus intensity level at which 50% of stimuli would be perceived. Tactile suppression during movement execution was used as a control measure. The main outcome measure of tactile suppression was the difference between perceptual thresholds at planning versus baseline (Planning), and execution versus baseline (Execution). We conducted a mixed ANOVA with 2 groups (Expert vs. Untrained) x 2 conditions (Planning vs. Execution). There was a main effect of condition ($F(1, 8) = 46.298$, $p<0.001$), no main effect of group ($F(1, 8) = 0.006$, $p = 0.940$), and no interaction effect ($F(1, 8) = 0.132$, $p = 0.726$). Preliminary findings in the sample tested thus far suggest that there is no difference in tactile suppression between expert pianists and musically untrained individuals. They suggest that suppression can occur in both experts and untrained individuals during movement planning, and that more suppression occurs during execution than planning. These findings contribute basic knowledge about tactile suppression during movement planning. This knowledge can serve as a stepping stone for future studies of the Touch Paradox, in which tactile suppression during planning can be studied for its relationship to motor performance outcomes.

**Disclosures: J. Tom:** None. **J.X. Manzone:** None. **J.L. Chen:** None.

**Poster**

**PSTR032. Movement Selection and Execution of Skilled Movements**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR032.03/CC10

**Topic:** E.04. Voluntary Movements

**Title:** Pointing in the dark

**Authors: *J. B. J. SMEETS**;
Vrije Univ. Amsterdam, Amsterdam, Netherlands

**Abstract:** If one tries to point straight ahead with an extended arm, one feels perfectly able to do so. What does one control when performing this task? One could assume that one would continuously monitor the perceived orientation of the arm and correct for any deviations from straight ahead (position control). Alternatively, one could move the arm into the desired orientation and subsequently keep it static (velocity control). These two strategies may seem equivalent at first sight, but they result in quite distinct behavior in the presence of noise. For position control, noise will result in fluctuations around an equilibrium posture. For velocity

control, in contrast, noise will result in a random walk of the arm. On average, this random walk will move the arm away from its initial orientation.
I measured the pointing behavior of blindfolded human participants, and determined various characteristics of the resulting trajectories, such as the Hurst exponent and how the average distance from the initial orientation and the variance depend on time. I found a Hurst exponent close to 0.5 and a variance that continuously increased with time. These results corresponded very well to simulations of a pure random walk combined with low-pass filtering. I found no evidence for a substantial contribution of position control, in contrast to the continuous use of position control in goal-directed movements.

**Disclosures: J.B.J. Smeets:** None.

**Poster**

**PSTR032. Movement Selection and Execution of Skilled Movements**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR032.04/CC11

**Topic:** E.04. Voluntary Movements

**Support:** FNRS COLLABORATEUR SCIENTIFIQUE FC 43127

**Title:** Task-dependent, flexible processing of sequence actions in fast trans-cortical feedback motor circuits.

**Authors: *H. KALIDINDI**, F. CREVECOEUR;
ICTEAM and Inst. of Neurosci., Univ. Catholique de Louvain, Louvain-la-Neuve, Belgium

**Abstract:** Everyday behavior involves performing a sequence of actions to achieve a goal. Sequence execution involves combining successive actions with shorter goals into larger actions. A fundamental question is whether sequence execution is a cognitive or a motor skill? Some studies show that individual movements are reshaped to maximize the efficiency of sequence as a whole, consistent with a transition from concatenation of independent components to holistic planning of the sequence. Alternatively, (Zimnik et al., 2021) showed that during rapid sequence execution, the second target is expressed late in the motor response, just before the completion of first reach, and interpreted late cueing as an external trigger applied to the motor system. It remains unknown whether late cueing of second target, and holistic sequence planning can be explained at the level of motor processing.To address this problem, we simulated a feedback controller controlling a point mass object in a two-reach sequence task. The simulations showed that the task objective – a requirement to stop/no-stop at first target – determined how much the control of first movement depended on the second target. When the agent was not required to stop at the first target, feedback gains throughout the first movement were tuned to the second target. Consequently, a perturbation applied early in the first movement produced different hand paths tuned to the second target. In contrast, when required to stop, dependency on the second target emerged near the end of the first reach. Importantly, both early reshaping and late cueing

emerged as optimal solutions of the control problem, and did not require any external trigger from an independent system. Thus, our simulations predicted that the instructions about the intermediate targets mediate how much the controller during the first reach depends on the second target, predictions that we validated experimentally. Human subjects (N=15) performed the two-reach task and showed early changes in kinematics dependent on the second target. Step-loads applied early in the first reach revealed that long latency feedback responses (LLFRs, 50-100 ms latency) were tuned to the second target. In a second experiment (N=14), subjects were asked to stop at the first target, and we observed that the change in kinematics related to the second target and differences in LLFRs disappeared as predicted in the model. Overall, we developed an ideal actor model of sequence execution and validated the model predictions with human experiments. The results suggest that disparate properties of sequence execution are a consequence of flexible, task-dependent processing in feedback motor system.

**Disclosures: H. Kalidindi:** None. **F. Crevecoeur:** None.

**Poster**

**PSTR032. Movement Selection and Execution of Skilled Movements**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR032.05/CC12

**Topic:** E.04. Voluntary Movements

**Support:** NIH-R37-HD087089
NIH-R01-CRCNS-NS120579
NSF-M3X-1825942

**Title:** Ringing a Bell: Human Control Strategies for Contact-Rich Physical Interactions

**Authors: *S. BAZZI**[1], S. ANNAPRAGADA[1], R. SHARIF RAZAVIAN[3], D. STERNAD[2]; [2]Departments of Biology, Electrical & Computer Engineering, and Physics, [1]Northeastern Univ., Boston, MA; [3]Northern Arizona Univ., Flagstaff, AZ

**Abstract:** In daily activities, humans constantly interact with complex objects, such as carrying a bag of groceries or a cup of coffee. Understanding the skillful control of these interactions is critical to advance our understanding of human motor control of natural behaviors. Our previous research 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. To address this question, human subjects were asked to ring a virtual bell, consisting of a clapper hanging inside a bell, that moved on a horizontal line. To interact with the bell-and-clapper system, humans moved a robotic manipulandum that also provided haptic feedback of the contact dynamics. Subjects were asked to ring at a stable

rhythm, both at a comfortable tempo and at a fixed frequencies signaled by a metronome; they were free to pick their movement amplitude. Subjects repeated 60 trials (20s duration) over 3 days; their kinematic and kinetic data were analyzed to determine their convergence toward a preferred pattern. Four control objectives were hypothesized: 1) subjects reduce effort by minimizing force 2) they exploit natural dynamics to minimize energy expenditure 3) they prioritize stability to reduce the impact of sensorimotor noise or 4) they maximize the predictability of the system. To test these hypotheses, we inverse-simulated the bell-clapper model, assuming sinusoidal bell motion on a horizontal line. Simulating over viable combinations of amplitudes and frequencies of bell movements, the expended force, energy, stability, and predictability were computed, leading to solution spaces that summarized 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 interaction 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 when contacts are added, the control objective tends towards minimization of interaction forces, possibly to minimize the unfavorable feeling of the collision.

**Disclosures:** **S. Bazzi:** None. **S. Annapragada:** None. **R. Sharif Razavian:** None. **D. Sternad:** None.

**Poster**

**PSTR032. Movement Selection and Execution of Skilled Movements**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR032.06/CC13

**Topic:** E.04. Voluntary Movements

**Support:** NIH-R37-HD087089
NIH-R01-CRCNS-NS120579
NSF-M3X-1825942

**Title:** Interactive perception in the human manipulation of complex objects

**Authors:** ***M. SADEGHI**[1], S. BAZZI[1], R. NAYEEM[1], R. SHARIF RAZAVIAN[2], D. STERNAD[1];
[1]Northeastern Univ., Boston, MA; [2]Northern Arizona Univ., Flagstaff, AZ

**Abstract:** Interactive multimodal perception is of paramount importance in the interaction with objects of unknown shape, material, and content. Object properties become particularly challenging for humans to learn if the object has internal dynamics; for instance, the sloshing liquid in a cup of coffee can generate complex interaction forces that need to be preempted, compensated, or corrected for. While humans can dexterously transport a cup filled with coffee, there is limited understanding about the control mechanisms and the contribution of different

sensory modalities to a successful action. This study investigated the effect of visual and haptic information on humans' exploratory interactions with a simplified 'cup of coffee', an object with nonlinear internal dynamics. Subjects were instructed to rhythmically transport a virtual cup with a rolling ball inside between two targets at a specified frequency, using a robotic interface. The cup and targets were displayed on a projection screen, and force feedback from the cup-and-ball dynamics was provided via the robotic manipulandum. Subjects were encouraged to explore and prepare the dynamics by 'shaking' the cup-and-ball system to find the best initial conditions prior to the rhythmic task. Two groups of subjects received full haptic feedback about the cup-and-ball dynamics during the task; however, for one group the ball and its movements were visually occluded, while the other group could see the ball. Analysis of kinematic and kinetic data showed that visual information about the ball movement had three distinctive effects on the performance: seeing the ball reduced preparation time needed to understand the dynamics, the exploratory movements converged faster towards the task-required rhythm, and, importantly, preparation led to simpler, more linear input-output interactions between hand and object. These findings highlight the roles of visual and haptic information in the interactive perception and exploration of complex objects.

**Disclosures:** **M. Sadeghi:** None. **S. Bazzi:** None. **R. Nayeem:** None. **R. Sharif Razavian:** None. **D. Sternad:** None.

**Poster**

**PSTR032. Movement Selection and Execution of Skilled Movements**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR032.07/CC14

**Topic:** E.04. Voluntary Movements

**Support:** NIH-R37-HD087089
NIH-R01-CRCNS-NS120579
NSF-M3X-1825942

**Title:** Managing self-generated interactive dynamics in the transport of complex objects

**Authors:** ***K. DESABHOTLA**[1], R. T. NAYEEM[1], M. SADEGHI[2], D. STERNAD[3];
[1]Electrical Engin., [2]Electrical & Computer Engineering; Biol., [3]Electrical & Computer Engineering; Biology; Physics, Northeastern Univ., Boston, MA

**Abstract:** When a waiter carries a cup of coffee in a café, they must swerve around tables to avoid collisions. In doing so, the waiter exerts forces onto the cup and coffee, which, in turn, act back on the hand. These internal dynamics can interfere with task goals, and, for example, coffee can spill from the cup. How do we deal with such internal dynamics that are generated by our own actions? Studies in motor control have examined how humans respond to perturbation during movement; however, the source of the perturbation has often been external. In naturalistic settings, self-generated dynamics are the more frequent scenario. Extending our previous work,

this study modeled a 3D cart-and-pendulum system moving in a horizontal plane, where the cart was displayed as a semi-spherical cup, and the pendulum bob was displayed as a ball rolling inside. The dynamics represent the challenges of transporting a cup of coffee: underactuation and nonlinearity. Subjects interacted with the system in a virtual environment, where they moved a displayed cup, and received haptic feedback via a robotic manipulandum. The task was to transport the cup and ball from a "home" position to a target and back, passing through a via point located lateral to the target direction. Subjects had to move as fast as possible without losing the ball, and task difficulty was manipulated by moving the via point farther from the home-target line. In a control condition, subjects also performed the task with a rigid cup, without any internal dynamics. We evaluated performance by analyzing movement path, duration, and smoothness, each assessed at early and late stages of practice and with regard to different via-points. We also evaluated the degree to which cup and ball behaved in-phase as a measure of predictable interactive dynamics during performance. Individuals converged to a variety of chosen movement paths, however, they all arrived at solutions that reduced movement time, and increased smoothness. Contrary to expectations, subjects achieved time-normalized-smoother movements in cup and ball condition, compared to the rigid-cup condition, although in exchange for longer movement durations. Additionally, the cup movement phase, as directly controlled by subjects, gradually evolved to match the ball movement phase, i.e., the internal dynamics, through practice. This indicated a strategy to keep both the actuated (cup) and underactuated (ball) dynamics synchronized to avoid self-induced disruptive internal dynamics. These results are first steps to shed light on how humans exploit the dynamics of objects to manage self-induced perturbations in their complex interactive experiences.

**Disclosures: K. Desabhotla:** None. **R.T. Nayeem:** None. **M. Sadeghi:** None. **D. Sternad:** None.

**Poster**

**PSTR032. Movement Selection and Execution of Skilled Movements**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR032.08/CC15

**Topic:** E.04. Voluntary Movements

**Support:** CRSNG Grant 418589

**Title:** Competitive processes in free-choice, action-based decisions: Effect of decisional uncertainty in an obstacle avoidance task

**Authors: *D. DELISLE-GODIN**[1], P.-M. BERNIER[2];
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**Abstract:** Decisions about actions are thought to arise from a competition between simultaneously activated movement plans, biased by variables such as movement costs, rewards

or task rules, until a threshold is reached and an action is executed. In support, reaction times (RT) are longer in situations of increased competition, such as during incongruent trials in Flanker tasks or equiprobable target locations (point of subjective equality; PSE) in hand selection tasks. Still, action competition has mostly been studied in contexts in which the target goal is instructed or in which overt execution of both responses is possible, limiting the evidence for a lower-level, action-based competitive process evolving within a single cortical hemisphere. Therefore, we aimed to investigate the effect of decisional uncertainty on RTs in a free choice task where overt execution of both responses was impossible. We developed an obstacle avoidance task in which healthy human participants (n = 11; preliminary results; n = 30; targeted sample) had to reach toward a visual target using their right (dominant) hand while avoiding an obstacle positioned along the movement path. Participants were free to avoid the obstacle to its left or its right but had to initiate their movement within 500ms of obstacle presentation. The target was positioned straight ahead of participants and remained unchanged across trials (400). Uncertainty was manipulated by placing a 9cm obstacle on participants' direct path to the target (i.e., at the PSE) (maximal uncertainty condition; 100 trials), or an 18cm obstacle shifted laterally by ±4.5cm from the PSE location (minimal uncertainty condition; 50 trials for both left and right). Importantly, this setup equated movement trajectories across conditions, allowing us to isolate the influence of uncertainty on RTs. Results revealed that RTs were significantly slower in the maximal uncertainty condition (375ms ± 32) as compared to the minimal uncertainty condition (355ms ± 28; $p$=0.0005). This suggests that a competitive process also underlies action-based free-choice decisions. In contrast, movement times did not differ across conditions (262ms ± 48 and 261ms ± 47 for maximal and minimal uncertainty conditions, respectively; $p$=0.97), supporting the similarity of movement kinematics. It has been proposed that pre-movement β activity could reflect response competition in the sensorimotor cortex but evidence to that effect remains contradictory and limited in action-based decisions. Considering that, collection and analysis of electrophysiological data is currently underway to investigate the modulation of β activity in our task.

**Disclosures: D. Delisle-Godin:** None. **P. Bernier:** None.

**Poster**

**PSTR032. Movement Selection and Execution of Skilled Movements**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR032.09/CC16

**Topic:** E.04. Voluntary Movements

**Support:** Newman Fund

**Title:** Velocity-level planning in human neuro-motor control: behavioral evidence based on brownian processes

**Authors:** *J. HERMUS[1], **F. TESSARI**[1], R. SUGIMOTO DIMITROVA[1], N. HOGAN[2]; [1]Mechanical Engin., [2]Mechanical Engin. and Dept. of Brain and Cognitive Sci., MIT, Cambridge, MA

**Abstract:** This work presents experimental evidence of pervasive Brownian processes in different human motor tasks ranging from static posture to continuous motion. Brownian processes, also known as random walks, are characterized by two distinctive signatures: (i) a power spectrum decaying at -20 decibels per decade; and (ii) an unbounded variance growing linearly with time. Such processes are inherently unstable and are apparently incompatible with common observations of human motor behavior; e.g., we can maintain upright posture without evidence of unbounded variance.

Three different motor tasks were investigated in healthy subjects: rotating a crank, maintaining a static hand posture, and maintaining upright standing posture. The first task was selected as it allows unbounded continuous motion within a finite configuration space. The second and third are instead representative of two common postural tasks involving the upper and lower limbs respectively.

All three tasks presented evidence of Brownian behavior. Nonetheless, only the crank turning task showed evidence of variance growing without bound since the task allowed for a limitless range of angular positions. In the postural tasks, the variance initially grew but reached a bound, in line with expectations. These results show that Brownian processes provide an adequate description of the observed positional data; however, some additional control action must limit the position variance during static posture.

Different models were implemented to identify a unifying descriptive motor control framework capable of reconciling the whole experimental evidence i.e., the presence of Brownian behavior with limited position variance in postural tasks and unbounded position variance in continuous motion tasks. The only model capable of reproducing all the observations required forward-path velocity commands corrupted by stationary noise. Moreover, we identified intermittent control actions as the key underlying mechanism to limit variance during postural tasks.

This work provides the first independent behavioral evidence supporting the theory that the central nervous system encodes motion commands in terms of velocity.

**Disclosures: J. Hermus:** None. **F. Tessari:** None. **R. Sugimoto Dimitrova:** None. **N. Hogan:** None.

**Poster**

**PSTR032. Movement Selection and Execution of Skilled Movements**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR032.10/CC17

**Topic:** E.04. Voluntary Movements

**Support:** Newman Fund
AI.D Grant 16ME0539K

**Title:** Exploring zero-force trajectories in constrained motions

**Authors: *E. SHAHRIARI**[1,2], S. HADDADIN[2], N. HOGAN[1];
[1]MIT, Cambridge, MA; [2]Tech. Univ. of Munich, Munich, Germany

**Abstract:** Humans excel at physically interacting with their environment. Yet it seems that to do so, they employ elementary dynamic actions that result in only "good-enough" control performance. In this work, we focused on constrained motions, specifically turning a horizontal crank. In previous work, we observed that forces generated by human subjects included unproductive normal force components that varied periodically with crank angle. Using a model of human interactive dynamics with observed normal forces and motions revealed roughly elliptical zero-force trajectories—hypothetical but well-defined trajectories that subjects would have followed in the absence of forces. In principle, a zero-force trajectory may be identified independent of interactive dynamics (Hogan 2014, 2017). In the current study, we aimed to verify the elliptical zero-force trajectories without making any modeling assumptions about human interactive dynamics. We reasoned that if the crank constraint path were deformed to match the estimated zero-force trajectory, normal forces should vanish. Conversely, if the crank constraint path were deformed to be orthogonal to the estimated zero-force trajectory, normal forces should be enhanced. 12 subjects turned a virtual crank, rendered by an InMotion robot, at a visually-instructed constant rotational speed. Unbeknownst to subjects, the constraint had three different shapes: (i) circular; (ii) elliptical (closely aligned to the previously estimated zero-force trajectory); and (iii) orthogonal to that ellipse. Subjects performed 45 trials, and from these trials, RMS normal forces were calculated. The mean RMS normal force increased (by factors of 10% and 40%) as the constraint deviated further from the zero-force trajectory ellipse. Post-hoc two-sample t-tests with Bonferroni correction were conducted to confirm that the observed increase in normal force was significant ($p < 0.001$). These findings support the hypothesis that humans tend to employ elementary “building-block” dynamic actions—in this case, oscillatory zero-force trajectories and mechanical impedances—even for complex actions. This “good-enough” control would incur a cost of decreased performance in some circumstances. As the intended action diverged more from the result of employing those “default” actions, performance deteriorated. **Hogan N**. A general actuator model based on nonlinear equivalent networks. *IEEE/ASME Trans Mechatronics* 19: 1929-1939, 2014.**Hogan N**. Physical interaction via dynamic primitives. In: *Springer Tracts in Advanced Robotics,* edited by Laumond JP, Lassere JB, Mansard N. Springer, 2017, p. 269-299.

**Disclosures: E. Shahriari:** None. **S. Haddadin:** None. **N. Hogan:** None.

**Poster**

**PSTR032. Movement Selection and Execution of Skilled Movements**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR032.11/CC18

**Topic:** E.04. Voluntary Movements

**Support:** NIDILRR [grant number 90REGE0004]

**Title:** Differential impacts of energetic rewards and penalty on arm choice

**Authors: *M. ALGHAMDI**[1], H. NGUYEN[2], R. SHADMEHR[3], S. LEE[4];
[1]Biomed. Engin., Catholic Univ., ALEXANDRIA, VA; [2]Biomed. Engin., the Catholic Univ. of America, Washington, DC; [3]Johns Hopkins Univ. Dept. of Biomed. Engin., Baltimore, MD; [4]Biomed. Engin., Catholic Univ. of America, Biomed. Eng., Washington, DC

**Abstract:** Choice of arm use is made by comparing energetic costs associated with using two arms. We previously showed that use of one arm can be promoted by reducing energy associated with using the arm (‘reward’ on using the targeted arm). Conversely, the arm use could also be promoted by increasing energy of using the other arm (‘penalty’ on using the other arm). It has previously been shown, however, that reward and penalty work fundamentally different when guiding motor adaptation. The question thus remains regarding their differential effects when used in a choice task; will the two contrasting approaches (reward vs. penalty) lead to a different behavioral adaptation (i.e., change in the arm choice) even when a similar level of effort asymmetry is implemented? To answer this question, fifteen neurologically-intact subjects participated in an experiment where they reached towards visual targets in a virtual-reality environment. Energetic cost of reaching was modulated either amplifying the range of motion (ROM) of their nondominant arm, or by reducing the ROM of their dominant arm. Three different levels of energy asymmetry were used for each condition (i.e., 25%, 50%, 75% increase in nondominant arm ROM; 5%, 10%, 15% decrease in dominant arm ROM). We found that reduction of the dominant arm ROM (penalty) leads to significantly larger changes in the nondominant arm use, when compared to the cases that similar levels of energy ratio were achieved by amplification of the nondominant arm ROM (reward); a significant difference was observed in the sensitivity of the arm use to the energy ratio between the conditions (% change in the arm use per 100% change in the energy ratio: 25±15% in the reward condition vs. 195±70% in the penalty condition; $p < 0.001$). In both conditions, when the data from all subjects were analyzed, a significant degree of reduction was observed only in the reaction time of the nondominant arm, while the difference in the dominant arm was not found significant. Interestingly, between-subject variability in the arm use changes could be explained by the change in the reaction time of dominant arm (penalized) in the penalty condition ($r = -0.38$; $p = 0.02$), but by the change in the reaction time of nondominant arm (rewarded) in the reward condition ($r = 0.36$; $p = 0.03$). For the arm choice task, therefore, the use of non-dominant arm can be promoted by imposing penalty on the dominant arm (energy increase), which in turn energizes the action ‘initiation’ of the non-dominant arm. Such indirect promotion appears to have a greater impact on arm choice than directly rewarding use of the nondominant arm (energy reduction).

**Disclosures: M. Alghamdi:** None. **H. Nguyen:** None. **R. Shadmehr:** None. **S. Lee:** None.

**Poster**

**PSTR032. Movement Selection and Execution of Skilled Movements**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR032.12/CC19

**Topic:** E.04. Voluntary Movements

**Support:** NSERC Discovery
NSERC CRC Tier 1 Research Chair

**Title:** Energy and Time unifiyes the control of reaching and walking

**Authors: *J. D. WONG**[1], A. D. KUO[2];
[2]Fac. of Kinesiology, [1]Univ. of Calgary, Calgary, AB, Canada

**Abstract:** Humans often use either the lower or upper extremities to perform point-to-point movements, for example reaching with the hand and walking to a destination. The speed trajectories for each movement type have characteristic features that are explained by disparate principles. Reaching movements seem to maximize accuracy, whereas walking movements appear to minimize energy expenditure, although neither explanation explains how the respective durations increase with distance. It seems reasonable that both movement types should share common principles, since humans often walk and reach to fetch objects beyond an arm's length. Here we show that a combined objective of Energy and Time explains movement trajectories, durations, and peak speeds of both reaching and walking. Both tasks have different dynamics that yield different predictions, tested experimentally by humans reaching a range of distances, and separately walking a range of distances, all at self-selected pace. All movements had modest accuracy requirements, and so accuracy was not predictive of either task. These results suggest that common principles may underlie point-to-point movements for both upper and lower extremities, making it unnecessary to treat the two as entirely distinct. Humans may value both Energy and Time regardless of how they get to a destination. The differences between reaching and walking in part due to their different dynamics. Much of the Energy of reaching is explained by the work and rapid force production needed to accelerate the limbs, here in the horizontal plane of a planar manipulandum supporting the arms. Much of the Energy of walking is for mechanical work performed by muscles to redirect the body center of mass between pendulum-like steps under gravity. All of these costs decrease in different ways with longer movement durations, opposed a Time trade-off proportional to movement duration with coefficient , a valuation of time. That valuation appears related to resting metabolic rate but also an individual's subjective movement preferences. Optimal control predicts the trajectories and other features reasonably well, but may be summarized by simple power laws as a function of movement distance. The prediction accuracies were reasonable, with $R^2 > 0.8$ for both movement types ($P < 0.001$ for all cases, reaching 5-50 cm $N=9$, walking 1.5-12.5 m N=10).

**Disclosures: J.D. Wong:** None. **A.D. Kuo:** None.

**Poster**

**PSTR032. Movement Selection and Execution of Skilled Movements**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR032.13/CC20

**Topic:** E.04. Voluntary Movements

**Title:** Effort has a greater impact in selecting a target for movement than re-selecting a target during movement

**Authors: *I. KURTZER**[1], I. QURESHI[1], E. ADHAMI[1], R. AHMED[1], J. CASHABACK[2], D. TANIS[1];
[1]Biomed. Sci., New York Inst. of Technol. - Col. of Osteo. Med., Old Westbury, NY; [2]Univ. of Delaware, Newark, DE

**Abstract:** Adaptive behavior requires selecting the best available option. Studies that examine target selection prior to reach initiation report a strong preference for the least effortful option. In contrast, studies that examine target re-selection during ongoing movement report a weak influence of relative effort. This pattern suggests that the behavioral context, selection before movement versus re-selection during movement, is an important influence on the weighting of effort in target preference. However, the contrasting studies also have different mechanical contexts which confound the issue. Here we report two experiments on target preference designed to have the same mechanical setting but different behavioral settings. Participants reached forward to a single target that was occasionally replaced by a target pair surrounding the original (± 1, 2, 3 cm), referred to as a "target split". Owing to the arm's inertial anisotropy, mid-reach redirections to the leftward targets involve more effort than redirections to the rightward targets. The average left-right difference in required torque was ~45% greater than our earlier study because of the arm configuration at the mid-reach **Location:** here 45° shoulder, 90° elbow; before 30° shoulder, 90° elbow. In Experiment 1 (n = 12), reach initiation was cued by the default target filling. The typical trial involved just this one target but for the randomly inter-mixed split trials two target options replaced the default after the hand moved ahead by 3 cm. In Experiment 2 (n = 12), the default target and two flankers were all visible and unfilled during a wait period. On typical trials, reach initiation was cued by the default filling and the flankers disappearing, whereas on split trials the flankers filled and the default disappeared. Thereby, participants could decide which flanker was preferred before moving. Experiment 2 also presented a via target directly between the start and default end target, which required a forward reach then lateral deviation like the motion pattern of Experiment 1; hence, the mechanical setting of the two experiments was similar. Participants showed a significant bias to the rightward/less effortful option in Experiment 1 unlike our earlier study of online decision-making: median = 65% (37 IQR) vs 52% (16 IQR), one-sided rank-sum test, p = .033. Experiment 2 resulted in even more bias than Experiment 1 - median = 89% (27 IQR), one-sided rank-sum test, p = .026. Taken together, our results indicate that effort influences re-selecting a target during movement but less than selecting a target before movement.

**Disclosures: I. Kurtzer:** None. **I. Qureshi:** None. **E. Adhami:** None. **R. Ahmed:** None. **J. Cashaback:** None. **D. Tanis:** None.

**Poster**

**PSTR032. Movement Selection and Execution of Skilled Movements**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR032.14/DD1

**Topic:** E.04. Voluntary Movements

**Title:** Online decisions during reaching automatically prefer the target option closest in proximity, color, and shape to the original

**Authors: *D. TANIS**[1], R. AHMED[1], T. SINGH[3], I. KURTZER[2];
[1]Biomed. Sci., [2]New York Inst. of Technol. - Col. of Osteo. Med., Old Westbury, NY;
[3]Pennsylvania State Univ., University Park, PA

**Abstract:** Environments with dynamically changing options may require us to abandon a pursued but voided target and re-select among others currently available. We recently showed that online decisions for reaching automatically select the target options that are nearest to the original. To better understand the inherent preferences of target re-selection, we examined the impact of color and shape, features known to strongly impact the efficiency of visual search but are processed relatively slowly through the ventral visual pathway. In Experiment 1 (n = 18), participants were instructed to ignore the color or shape of the new target options and reach to the one nearest the original (1 cm versus 3 cm). In Experiment 2 (n = 12) and Experiment 3 (n = 12), participants were instructed to ignore the proximity of target options (1 cm versus 3 or 5 cm) and reach to the target having the same color or shape, respectively, as the original. In Experiment 1, initial error rates were higher to the instructed near-target when its color was incongruent with the original target - Δ19% (26% SD), $p = 0.0015$. And even when correct, the online reaction times (oRTs) were slowed - Δ30 ms (43 ms SD), $p < 0.001$. There was a similar trend for target shape although the difference in oRTs did not obtain significance - 7% (15% SD), $p = 0.0385$; Δ10ms (12 ms SD), $p = 0.103$. Experiment 2 and 3 complemented these results. When instructed to obtain the target with the same color, then oRTs were modestly slower when the correct target was the further option - Δ13 ms (15 ms SD), $p = 0.00726$, and no effect on initial error rates was found - Δ1% (13% SD), $p = 0.7862$. A stronger impact of proximity was present in Experiment 3, where initial errors were greater when the correctly shaped target was the further option, Δ7% (10% SD) $p = 0.0097$, and oRTs were slower to the further option - Δ16 ms (20 ms SD), $p < 0.001$. Together these results show that the target option closest to the original target (in both location and visual features) is automatically preferred during online decision-making, consistent with the notion of a priority map for organizing behavior.

**Disclosures:** **D. Tanis:** None. **R. Ahmed:** None. **T. Singh:** None. **I. Kurtzer:** None.

**Poster**

**PSTR032. Movement Selection and Execution of Skilled Movements**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR032.15/DD2

**Topic:** E.04. Voluntary Movements

**Support:** NIH Grant R01 NS111148

**Title:** Direction-independent stiffness regulation in a challenging ballistic release task highlights human neuro-motor performance limitations

**Authors: *F. TESSARI**[1], C. ZHANG[3], H. AKOLKAR[3], J. HERMUS[1], N. HOGAN[1,2], A. B. SCHWARTZ[3];
[2]Brain and Cognitive Sci., [1]MIT, Cambridge, MA; [3]Univ. of Pittsburgh, Univ. of Pittsburgh, Pittsburgh, PA

**Abstract:** In this work we investigate the human ability to predictively generate task-specific impedance, and specifically stiffness, to complete a challenging ballistic release task in multiple directions. The task required subjects to exert a given force against a physical constraint, and - when the constraint was suddenly released - they were instructed to reach a pre-defined specific target position aligned with the direction of the applied force. The experimental task was designed to heavily penalize corrective actions, thus encouraging subjects to pre-set their arm impedance to successfully complete the task. Data from 20 healthy subjects were collected while performing the ballistic release task in a horizontal plane in four different directions (forward, backward, left and right) while the arm was held in a gravity-neutral configuration. In each direction, multiple target forces (15, 20, 25 N) and reaching displacements (2.5, 5, 7.5 cm) were tested. Each of the nine possible force-displacement configurations was repeated 9 times. The task nominal end-effector stiffness ranged from 200 to 1000 N/m. The arm end-effector position and force were measured and used to identify the arm end-effector impedance by fitting these data to a second order dynamical system (mass, spring, and damper). This model proved to be the most parsimonious capable of correctly describing the whole experimental evidence. Subjects completed the task in all required directions and force-displacement combinations. The identified stiffness showed that subjects could generate the required nominal task stiffness independently from the direction of motion. This is particularly interesting because it suggests the capability of subjects to adapt to the high directionality of the arm end-effector stiffness ellipse. Moreover, the stiffness estimates highlighted the subjects' preference to complete the task with the minimum possible stiffness for every force-displacement combination. This supports the hypothesis of an effort minimization strategy in stiffness generation. More importantly, subjects proved to be limited, not by the amount of required force (all subjects could generate the maximum target force), but only by the amount of end-effector stiffness they had to produce (higher failure rates were observed in higher stiffness conditions). This supports the observation that in some physical interaction circumstances, especially pushing, human neuro-muscular performance is not limited by force exertion but by stiffness production.

**Disclosures: F. Tessari:** None. **C. Zhang:** None. **H. Akolkar:** None. **J. Hermus:** None. **N. Hogan:** None. **A.B. Schwartz:** None.

**Poster**

**PSTR032. Movement Selection and Execution of Skilled Movements**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR032.16/DD3

**Topic:** E.04. Voluntary Movements

**Title:** Task-dependent stiffness is independent of movement direction and muscle activation

**Authors: *H. AKOLKAR**[1], C. ZHANG[2], F. TESSARI[4], J. R. HERMUS[4], N. HOGAN[4], A. B. SCHWARTZ[3];
[1]Neurobio., [2]Univ. of Pittsburgh, [3]Dept. of Neurobio., Univ. of Pittsburgh, Pittsburgh, PA; [4]MIT, MIT, Cambridge, MA

**Abstract:** Our recent study has shown that humans can predictively control their arm end-point impedance in a challenging ballistic release task in different movement directions and arm configurations. Subjects could successfully perform this task primarily by tuning their arm stiffness. Subjects were required to hold a handle at a certain force level against a robot arm for a random duration, at which point the robot resistive force was set to zero, triggering a ballistic movement. Subjects then arrested the handle within a target displacement to succeed in the task. Any corrective movement during or after the ballistic release was penalized. The task was performed in a horizontal plane spanning four orthogonal directions: rightward, leftward, forward and backward. Three force and three displacement targets were presented, leading to nine levels of stiffness conditions. Surface EMG was recorded from eight muscle groups - wrist Flexor (Flexor carpi radialis, FCR) and Extensor (Extensor carpi ulnaris, ECU), Bicep (Biceps brachii, short head), Tricep (Triceps brachii, long head), anterior (Deltoid, anterior head) and posterior Deltoid (Deltoid, posterior head) and Pectoralis (Pectoralis major) and Trapezius (Trapezius). Principal Component Analysis of the recorded EMG during the force-hold, pre-movement phase showed that muscle activity was largely contained in at most three, and sometimes only in two, of the potential eight dimensions. Interestingly, the angle between these subspaces (a measure of similarity) for different pairs of conditions such as direction, force and displacement were found to be close to $\pi/2$, indicating vastly varied muscle activations across conditions. Moreover, single and multi-variate linear models were used to fit the EMG activity and task parameters. This analysis showed that the EMG signals fit the target force (R-squared: 0.76) and nominal stiffness (R-squared: 0.62) better than target displacement (R-squared: 0.39). EMG in the force null-space (EMG data projected onto the null-space of the matrix obtained from linear fit between force and EMG) also fit stiffness better than displacement. This shows that subjects could tune their pre-movement muscle activity to achieve both the required target force as well as the task-related stiffness through co-activation of different pairs of muscles. They could achieve these results despite the different muscle configurations required in different directions of motion.

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**Poster**

**PSTR032. Movement Selection and Execution of Skilled Movements**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR032.17/DD4

**Topic:** E.04. Voluntary Movements

**Support:** NIH Grant NS111148

**Title:** Direction-independent impedance in non-human primates

**Authors: *C. ZHANG**[1], H. AKOLKAR[2], J. R. HERMUS[3], F. TESSARI[3], N. HOGAN[3], A. B. SCHWARTZ[2,1];
[1]Dept. of Bioengineering, [2]Dept. of Neurobio., Univ. of Pittsburgh, Pittsburgh, PA; [3]MIT, Cambridge, MA

**Abstract:** We are interested in whether subjects can preset the impedance of their arms to achieve near-ballistic, accurate reaches in different directions. To test this idea, we designed a task in which subjects pushed a manipulandum against various levels of resistance which were suddenly released. Successful trials required terminating the movement at specific distances without corrections. Two rhesus monkeys (*Macaca mulatta*) were trained to grasp a force-sensing manipulandum on a linear track. They exerted a specified level of isometric force in a specific direction on a fixed handle for a random duration. The handle was then released, producing a near-ballistic movement. The monkeys were rewarded for stopping the handle in a target range within a limited time. Force and displacement were shown in real-time on a screen in the form of cursor position. We recorded force and displacement data as monkeys performed the task. We have also collected neural and muscle data in one monkey. Single-unit neural activity was recorded using a Utah array implanted in primary motor cortex. Surface EMG was recorded from six electrodes placed on three pairs of antagonist arm muscles corresponding arm and wrist movements. A 2$^{nd}$-order dynamical system (mass, spring and damper) was used to estimate the endpoint impedance based on the force and displacement of the hand. Consistent with our human study [Tessari et al., SfN 2023], stiffness was correlated with both the target force and displacement task conditions across directions. Muscle activity was found to vary across directions, and single unit neural activity was found to modulate with task parameters such as force, displacement, and direction. Grant: R01 #NS111148 funded by National Institute of HealthRef: Tessari F. et al., Direction-independent stiffness regulation in a challenging ballistic release task highlights human neuro-motor performance limitations, Neuroscience 2023, Society for Neuroscience

**Disclosures: C. Zhang:** None. **H. Akolkar:** None. **J.R. Hermus:** None. **F. Tessari:** None. **N. Hogan:** None. **A.B. Schwartz:** None.

**Poster**

**PSTR032. Movement Selection and Execution of Skilled Movements**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR032.18/DD5

**Topic:** E.04. Voluntary Movements

**Support:** University of North Georgia Presidential Semester Award

**Title:** The Effect of Handedness on Interlimb Asymmetries and Hand Selection Behavior - Reduced Dominant Arm Bias in Left Handers

**Authors: *A. SALAMI**, S. MISKO, M. SMITH, A. PRZYBYLA;
Dept. of Physical Therapy, Univ. of North Georgia, Dahlonega, GA

**Abstract:** Previous research on interlimb asymmetries in reaching movement performance have shown unique characteristics of the dominant and nondominant arms for movement control. While most studies tested right handed individuals, our previous study in left handers showed similar characteristics but with significantly reduced interlimb asymmetries. This reduction was due to the right nondominant arm superior performance over the left nondominant arm in right handers. Other studies in right handers showed that interlimb asymmetries associate with hand selection behavior. For example, reduced interlimb asymmetries by occlusion of visual feedback during movement or a long-term sports training led to a relative decrease in the right dominant arm bias during hand selection tasks in right handers. We now ask whether left handers show reduced left dominant arm bias in hand selection behavior. To date, 16 left-handed and 6 right-handed healthy young volunteers completed the hand selection task consisting of 12 blocks of 20 trials each to pseudorandomized targets distributed systematically in the frontal space. In addition, they have also completed non-choice unimanual reaching tasks to assess their arms movement performance and determine the level of interlimb asymmetries. Preliminary results showed that, like in right handers, there is a significant dominant (left) arm bias in selection frequency (58% vs. 50%, $t_{1,15} = 6.6$, $p < .0001$). However, this dominant (left) arm bias in left handers is significantly smaller than observed in the prior study the dominant (right) arm bias in right handers (58% vs. 68%, $t_{1,15} = 8.2$, $p < .0001$). These results show reduced bias for dominant arm selection in left handers and indicate a plausible association with interlimb asymmetries, which are also reduced. These findings suggest a significant effect of handedness in hand selection behavior, which should be taken into consideration when tailoring sports training or rehabilitation to left handers.

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**Poster**

**PSTR032. Movement Selection and Execution of Skilled Movements**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR032.19/DD6

**Topic:** E.04. Voluntary Movements

**Support:** University of North Georgia Presidential Semester Award

**Title:** Reduced Dominant Arm Bias in Virtual Reality Reaching Task - A Novel Tool for Assessment of Hand Selection Behavior.

**Authors:** K. GIBSON, T. HALL, M.-K. HOPKINS, R. HUDGINS, A. WILLMAN, S. SOLNIK, ***A. PRZYBYLA**;
Physical Therapy, Univ. of North Georgia, Dahlonega, GA

**Abstract:** Previous research on interlimb asymmetries in reaching movement performance have shown distinct specialization of the dominant and nondominant arms for movement control. More recent studies showed that these interlimb asymmetries associate with hand selection behavior. For example, a reduction in asymmetries by occlusion of visual feedback during movement or a long-term sports training leads to a relative decrease in the dominant arm bias during hand selection tasks. Our understanding of hand selection behavior and underlying neural mechanisms could help with development of novel approaches to sports training or rehabilitation. In this study we developed a novel virtual reality (VR) application to test hand selection behavior. Ultimately, we aim to develop a reliable VR tool to provide athletic trainers and rehab clinicians with a quick and easy assessment of hand selection behavior. To date, 40 healthy young volunteers completed the hand selection task consisting of 20 blocks of 18 trials each to pseudorandomized targets (balloons) distributed systematically in the frontal space. Preliminary results showed that there is a significant bias towards the dominant arm in selection frequency (55% vs. 50%, $t_{1,38} = 2.7$, $p < .01$). However, this dominant arm bias is significantly smaller than observed in the prior study using non-VR experimental setup (55% vs. 68%, $t_{1,38} = 7.7$, $p < .001$). These findings suggest that interlimb asymmetries in 3D VR environment are likely to be smaller. This is consistent with previous observations of reduced asymmetries in a less constrained 3D space.

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**Poster**

**PSTR032. Movement Selection and Execution of Skilled Movements**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR032.20/DD7

**Topic:** E.04. Voluntary Movements

**Support:** Ontario Research Fund
VISTA York University
Baycrest Hospital

**Title:** Utility of mobile visuomotor assessment for neuropsychological evaluation in older adults

**Authors: *G. ADIBMORADI**[1], S. MCCOLL[2], D. SODUMS[2], N. D. ANDERSON[2], J. D. RYAN[2], L. E. SERGIO[1];
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**Abstract:** ***Background:*** The ability to perform visually-guided motor tasks requires the transformation of visual information into programmed motor outputs. When the guiding visual information does not align spatially with the motor output (cognitive motor integration, CMI) , the brain processes rules to integrate the information for an appropriate motor response. Performance on such tasks is affected in individuals at risk of and in the early stages of dementia, and may affect their activities of daily living. Using mobile technology with older individuals may provide us with a more sensitive and accessible metric for assessing cognitive and functional motor abilities, when compared to traditional neuropsychological assessments. Here, we investigate the relationship between a traditional neuropsychological test battery and tablet-based visuomotor skill performance. ***Methods:*** 38 participants, between the ages of 56 and 86, ranging from healthy to early Alzheimer's disease completed the WMS-IV neuropsychological test battery which took about 180 minutes. They also performed three tablet-based tasks that tested the participants' CMI abilities which took about 15 minutes. Specifically, participants performed 1) a standard condition requiring direct interaction with visual targets on a touchscreen, 2) a CMI condition requiring one level of decoupling in which movements on the tablet had reversed visual feedback, and 3) a CMI condition requiring two levels of decoupling in which the finger was moved on the lower half of the screen, while moving the cursor to targets with reversed visual feedback on the upper half of the screen. Thus, there was a spatial dissociation between the gaze and hand movement. Outcome variables included reaction time, movement time, accuracy, precision, path length, and number of direction reversals. ***Results:*** Using a hierarchical linear regression analysis, we observed that 5 of our 6 CMI outcome measures were predictive of four tests from the WMS-IV battery, once variability for sex and age were accounted for ($p<0.05$). These tests include measures related to visuospatial skills, executive function, and memory. ***Conclusions***: Our findings suggest that, to some extent, mobile technology that involves multi-domain cognitive-sensory-motor processing may provide feasible, automated, and remotely deployable assessment alternatives to the current standard methods.

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**Poster**

**PSTR032. Movement Selection and Execution of Skilled Movements**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR032.21/DD8

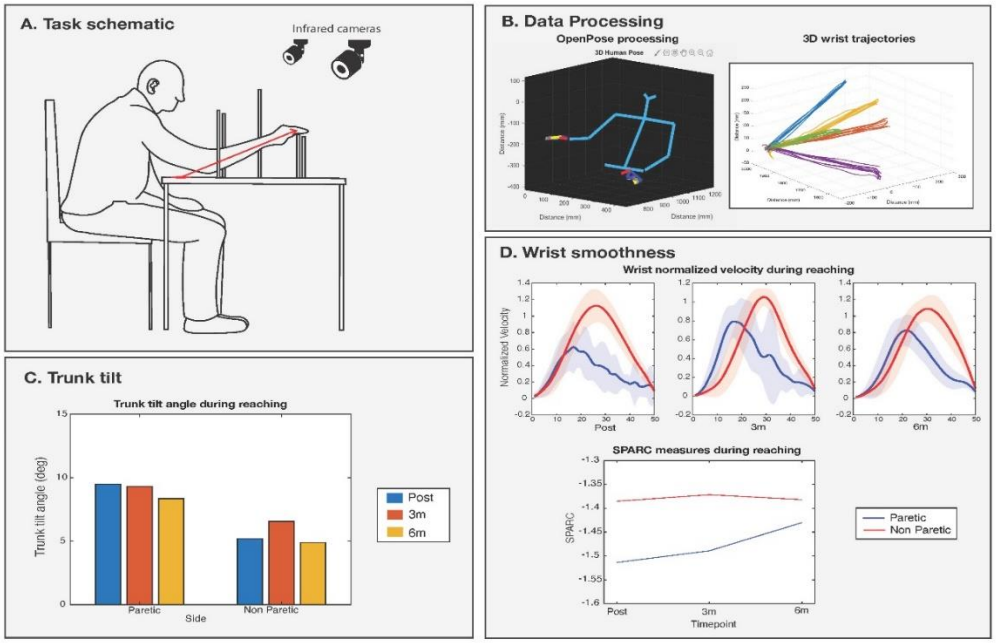
**Topic:** E.04. Voluntary Movements

**Support:** Health Research Council New Zealand 20-190

**Title:** The use of reach kinematics to distinguish between recovery phenotypes after stroke

**Authors: L. DUVAL**[1], A. ARAC[3], J. W. KRAKAUER[4], *C. M. STINEAR[2], W. BYBLOW[1]; [1]Exercise Sci., [2]Med., Univ. of Auckland, Auckland, New Zealand; [3]Neurol., UCLA, Los Angeles, CA; [4]Med., Johns Hopkins Univ., Baltimore, MD

**Abstract:** Early kinematic analysis may provide insight into upper limb motor recovery after stroke. Movement smoothness is an indicator of motor coordination and proficiency. Stroke survivors often exhibit jerky movements with the paretic upper limb. Trunk displacement may also increase to overcome shoulder-elbow flexion synergy during reaching. These deficits are well-understood at the chronic stage but less so at the sub-acute stage. It is possible to predict upper limb functional outcomes of individual patients within the first 2 weeks of stroke using the PREP2 prediction tool. PREP2 sequentially combines clinical, demographic and neurophysiological assessments. Although PREP2 has an overall accuracy of 75%, patients who are predicted to make a good recovery either achieve the predicted outcome by 12 weeks (good recovery), take longer than expected to reach the predicted outcome (late recovery), or do not reach their predicted outcome (poor recovery). Our study examines kinematic measures of reaching movement smoothness with the paretic upper limb and trunk displacement for distinguishing between these recovery phenotypes. As part of an ongoing registered clinical trial, data from 20 participants were randomly selected for analysis. Kinematic and clinical assessments were made at 4, 12, and 26 weeks post-stroke. Data from one participant shown in Figure (Male 73y, Day3 SAFE=1, ARAT=4, MEP$^{+}$, 12w ARAT=39, Good Recovery). **A.** Fifty reaches were made in separate blocks with either the paretic or non-paretic side. **B.** Data processing was undertaken using OpenPose to compute 3-D reach trajectories. **C.** Trunk tilt angle was calculated between the start and end of reach. **D.** Spectral arc length (SPARC) quantified smoothness of the wrist trajectory. A linear mixed-effect model investigated effects of time and recovery phenotypes. SPARC increased and trunk tilt angle reduced over time and interacted with recovery phenotype. Prediction of upper limb outcome after stroke may benefit from early reaching kinematic analyses.



**Disclosures:** **L. Duval:** None. **A. Arac:** None. **J.W. Krakauer:** None. **C.M. Stinear:** None. **W. Byblow:** None.

**Poster**

**PSTR032. Movement Selection and Execution of Skilled Movements**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR032.22/DD9

**Topic:** E.04. Voluntary Movements

**Support:** ISF 1684/20

**Title:** Extracting motor commands from zebrafish natural behavior - a dynamical control theory approach

**Authors:** ***Y. RUBINSTEIN**[1], S. SHAPIRA[4], M. MOSHKOVITZ[2], Y. HENDEL[4], S. TIOMKIN[5], L. AVITAN[3];
[2]The Hebrew Univ. of Jerusalem, [3]Hebrew Univ. of Jerusalem, [1]Hebrew Univ. of Jerusalem, Jerusalem, Israel; [4]The Hebrew Univ. of Jerusalem, Jerusalem, Israel; [5]San Jose state Univ., San Jose, CA

**Abstract:** The repertoire of a freely behaving animal is traditionally characterized by extracting dozens of features of the body and clustering movements based on similarities in feature distributions. These clusters divide the continuous space of movements into a discrete set of movement types, where the set size depends on the clustering features. Such descriptive approaches are unable to provide meaning to the differences between individual movements, lack a mechanism underlying movement generation, and provide limited insights on movement neural control - all are gateways to understand the principles of movement sequencing.
Here, we treated freely behaving larval zebrafish movements as a response of a dynamical system to a sparse control signal. We modeled the system transfer function as a pair of differential equations implementing a low-level internal oscillator with feedback on its amplitude, and a high-level control signal which represents the decision. The model reliably reconstructed the complete spatio-temporal tail dynamics of 82% of movements.
Our model reduces sequences of complex high-dimensional movements into sparse low-dimensional control signals. These low-dimensional signals have simple and intuitive interpretation, allowing a meaningful comparison between single movements. Moreover, these signals suggest an efficient neural representation of movements, and predict neural control strength and onset time, as well as neural oscillation frequency. Together, the model provides a firm basis for understanding decision making and movement generation processes, from both experimental and theoretical perspectives.

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**Poster**

**PSTR032. Movement Selection and Execution of Skilled Movements**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR032.23/DD10

**Topic:** E.04. Voluntary Movements

**Support:** NSF CAREER 1943712

**Title:** Using stochastic optimal open-loop control to design robot-aided neuroimaging experiments that aim to identify the neural substrates of force and impedance control of the wrist

**Authors: *K. SCHMIDT**[1], B. BERRET[3], F. SERGI[2];
[1]Mechanical Engin., [2]Univ. of Delaware, Newark, DE; [3]Univ. Paris-Saclay, Paris, France

**Abstract:** Humans have a remarkable ability to control their physical interaction with the environment across a wide range of tasks, but our understanding of how these motor commands are controlled by the central nervous system remains limited. Impedance control plays a significant role in the control of wrist movements during dynamic perturbations even when alternative control strategies, such as torque control, are possible (Farrens et al. 2023). This suggests that torque and impedance control can act simultaneously, thus making it difficult to dissociate the contributions of different brain regions to each process independently. To overcome this, we are using a neuromuscular model to predict the activation response to different tasks, as a first step towards optimizing the design of an fMRI study that aims to identify the neural correlates of wrist torque and stiffness in healthy individuals.
While most neuromuscular models based on optimal control cannot predict muscle impedance, the Stochastic Optimal Open-Loop Control (SOOC) framework (Berret and Jean, 2020) was developed to account for both torque and impedance control. SOOC models the dynamical uncertainty to predict optimal muscle responses for a given task by minimizing effort and variance. While SOOC was originally developed for whole-arm reaching movements, we modified SOOC to a 2-DOF wrist task, and we tested the model with three force conditions (no force, constant force, divergent force), which were selected to elicit different levels of wrist torque and stiffness.
One key prediction of SOOC is that torque and stiffness responses are coupled under increases in perturbation amplitude in the presence of sufficient motor noise. For example, in the constant force condition, an increase in perturbation amplitude of 0.1 Nm (16.7% increase from 0.6 Nm) would result in an increase in joint torque of 0.1 Nm (27.9% increase) and joint stiffness of 0.36 Nm/rad (5.9% increase). Similarly, increasing constant and signal-dependent motor noise also increases optimal stiffness (sensitivity of constant noise: 20.11, $p<0.0001$; signal-dependent noise: 6.98, $p<0.0001$). The relative cost of final variance relative to effort costs also has a positive relationship with optimal stiffness (sensitivity: 0.91, $p<0.0001$).
We are now validating these predictions with behavioral task data, where we are measuring torque and stiffness via electromyography placed on four wrist muscles. Our goal is to define model-informed experimental conditions such that we can decouple the expression of joint torque and stiffness to use in a later fMRI study.

**Disclosures:** **K. Schmidt:** None. **B. Berret:** None. **F. Sergi:** None.

**Poster**

**PSTR033. Respiratory Control**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR033.01/DD11

**Topic:** E.08. Respiratory Regulation

**Support:** National Institute of Neurological Disorders and Stroke Grant K08 NS112573 01

**Title:** Amplitude of auditory evoked potentials depends on the phase of respiration.

**Authors: *Y. NA**, S. KUMAR, C. KOVACH, A. RHONE, B. DLOUHY;
Neurosurg., Univ. of Iowa, Iowa City, IA

**Abstract:** Several studies have shown that spontaneous respiration modulates neural oscillations across a wide network of brain areas including sensory cortex. One implication of this coupling between respiration and brain activity is that the excitability of the sensory cortex fluctuates with phase of respiration. We tested this hypothesis in the auditory cortex by measuring sound-evoked response and evaluating if the amplitude of this response had a systematic relation with the phase of respiration. We recorded 64-channel electroencephalography (EEG) signals from an adult participant and intracranial EEG from an epileptic patient in response to a 1 kHz pure tone [100ms duration, 1.5 to 3s ISI]. Subjects listened to the tones without any task while the respiration signal was being simultaneously acquired using an abdomen belt. After a total number of 750 trials in the EEG and 600 trials in the intracranial EEG were presented, trials were sorted according to the phase of respiration at the tone onset. Linear regression models, with phase of respiration as explanatory variable and single trial tone evoked potential as outcome variable, were fitted at every time point spanning 200ms before and 500ms after the tone onset. Responses at all electrodes of the EEG and 4 contacts from the Heschel's gyrus (HG) in the intracranial EEG were considered for analysis. We found that amplitudes of evoked responses at Parieto-temporal sites in the EEG and contacts at posteromedial HG (primary auditory cortex) in the intracranial EEG were statistically significantly related to phase of respiration around 200ms post-stimulus onset. Plot of event related potentials vs phase of respiration showed that magnitude of the evoked response was stronger during the inhalation phase of respiration. Our pilot data confirms the hypothesis. Further data collection is in progress to test the neurophysiological, perceptual, and behavioral consequences of variation of excitability of the auditory and other sensory cortices including visual with the phase of respiration.

**Disclosures:** **Y. Na:** None. **S. Kumar:** None. **C. Kovach:** None. **A. Rhone:** None. **B. Dlouhy:** None.

**Poster**

**PSTR033. Respiratory Control**

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**Program #/Poster #:** PSTR033.02/DD12

**Topic:** E.08. Respiratory Regulation

**Support:** HL122358 (MRH)
FAPEMIG (APQ-00779-21)
CNPq (200334/2022-0)

**Title:** Repeat audiogenic seizures in Sprague-Dawley rats with Kcnj16 mutations lead to ventilatory dysfunction

**Authors: *P. G. BITTENCOURT-SILVA**[1,3], W. A. OSMANI[1], M. LOWE[1], R. TAYLOR[1], L. ZANGL[1], M. EILBES[1], A. GALLO[1], D. COOK-SNYDER[1], G. MOURADIAN[1], H. FORSTER[1,4], G. S. F. DA SILVA[3], M. R. HODGES[1,2];
[1]Physiol., [2]Neurosci. Res. Ctr., Med. Col. of Wisconsin, Milwaukee, WI; [3]Physiol. and Biophysics, Federal Univ. of Minas Gerais, Belo Horizonte, Brazil; [4]Zablocki VAMC, Milwaukee, WI

**Abstract:** Epilepsy is a neurological disease characterized by the recurrence of seizures. Repeated generalized tonic-clonic seizures (GTCSs) have been shown to cause apneas and ventilatory chemoreflex impairment and are also associated with a greater risk for Sudden Unexpected Death in Epilepsy (SUDEP). However, the pathophysiological consequences of repeated seizures resulting in SUDEP, including respiratory dysfunction, remain unclear. Previous data from our lab showed that knockout of *Kcnj16* (which encodes $K_{ir}5.1$ channel subunits) in Dahl Salt Sensitive rats ($SS^{kcnj16-/-}$) led to sound-induced (audiogenic) seizures, which when repeated (1/day for 10 days) caused ictal apnea, progressively greater post-ictal respiratory suppression and increased seizure-related mortality. Here we characterized the effects on respiratory control of repeated seizures in three different *Kcnj16* mutations in a non-hypertensive genetic background (Sprague Dawley; SD). We tested the hypothesis that Kir5.1 mutations SD rats would lead to susceptibility to audiogenic seizures, which when repeated would cause a progressive post-ictal respiratory depression and high mortality. Breathing in 3 homozygous mutant lines of $SD^{KCNJ16\ -/-}$ males was measured *via* whole-body plethysmography before, during and after an acoustic stimulus (2 min) to elicit a seizure once a day for 10 days. Our preliminary results show that M7, M8 and T64I $SD^{Kcnj16-/-}$ rats experience audiogenic GTCS with ictal apnea as predicted. However, we did not observe seizure-related mortality after repeated seizures in the all three lines of $SD^{Kcnj16-/-}$ rats. Post-ictal respiratory suppression was also observed in all 3 strains of $SD^{Kcnj16-/-}$ rats but the degree of depression was less than $SS^{kcnj16-/-}$ rats. Interestingly, after 10 days of repeated seizures, baseline pulmonary ventilation ($V_E$) was increased 57.1% in the T64I strain (n=3), 64.7% in the M8 (n=4) and 92.1% in M7 (n=4) mainly due increase in tidal volume. Additionally, all rats homozygous mutant SD lines tested showed an increased $V_E/VO_2$ ratio after the 10 days seizure protocol, indicating that repeated seizures induced hyperventilation. Overall, our results show that $SD^{Kcnj16-/-}$ mutant rats also experience

audiogenic seizures but that the effects of repeated seizures are less severe than SS$^{kcnj16-/-}$ rats likely due to differences in the genetic backgrounds.

**Disclosures:** **P.G. Bittencourt-Silva:** None. **W.A. Osmani:** None. **M. Lowe:** None. **R. Taylor:** None. **M. Eilbes:** None. **A. Gallo:** None. **D. Cook-Snyder:** None. **G. Mouradian:** None. **H. Forster:** None. **G.S.F. da Silva:** None. **M.R. Hodges:** None.

**Poster**

**PSTR033. Respiratory Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR033.03/DD13

**Topic:** E.08. Respiratory Regulation

**Support:** National Institute of Neurological Disorders and Stroke Grant K08 NS112573 01

**Title:** Representation of respiration in the thalamus revealed by intracranial recordings in humans

**Authors: *S. KUMAR**, A. RHONE, C. KOVACH, M. MOWLA, A. CHAN, J. WEMMIE, G. RICHERSON, B. J. DLOUHY;
Univ. of Iowa, Iowa City, IA

**Abstract:** It is well known that the thalamus acts as a ‘gateway’ to relay sensory signals from the external world to the cortex. However, its role with respect to signals from the internal body such as respiration is not understood. Although a few studies in animals have shown that thalamus represents state of respiration [Chen et al, 1992, PMID: 1455102] and that it can inhibit spontaneous respiration when stimulated electrically [Baird et al, 1951 PMID: 14948448], evidence for relation between respiration and activity of the thalamus in humans remains scarce. We recorded local field potentials (LFPs) from the thalamus in 3 human patients with intractable epilepsy undergoing intracranial EEG for seizure focus localization. Recordings were made in the operating room while the patients were (i) breathing spontaneously in fully awake state (ii) breathing spontaneously without any support in general anesthesia induced unresponsive state and (iii) breathing with ventilator support in anesthetized and paralyzed state. Across all subjects, data from 19 bipolar contacts covering the anterior-posterior and dorsal-ventral axis of the thalamus were recorded. Respiration signal was recorded using abdomen belt. Data analysis was performed at each contact separately calculating power spectral density, coherence, and Granger causality between the respiration and LFP. In the awake state, 6 out of 19 showed statistically significant coherence between respiration and LFP with direction of causality ‘from respiration to the LFP’. When spontaneously breathing under anesthesia, a similar number (7 out of 19) showed significance coherence between respiration and LFP with the direction of causality remaining the same as in the awake state. However, none of the contacts showed significant coherence or causality between the respiration and LFP when breathing with ventilator support.

Our data suggests that rhythm of spontaneous respiration both under the awake and unresponsive state is represented in the thalamus. However, its absence of representation when breathing with ventilator support implies that this representation is not due to bottom-up sensory effects (e.g., of lung contractions) but is possibly due to an efferent copy from the brainstem respiratory oscillator.

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**Poster**

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**Program #/Poster #:** PSTR033.04/DD14

**Topic:** E.08. Respiratory Regulation

**Support:** NINDS K08 NS112573 01

**Title:** Neural correlates of breathing during awake, sleep, anesthetized, and ventilated states

**Authors: *M. MOWLA**[1], A. E. RHONE[1], S. KUMAR[1], C. KOVACH[1], G. RICHERSON[2,3], J. WEMMIE[4,5], A. CHAN[4,6], H. KAWASAKI[7,1], M. HOWARD III[1,7], B. J. DLOUHY[1,7,8]; [1]Dept. of Neurosurg., [2]Dept. of Neurol., [3]Dept. of Neurosci., [4]Dept. of Psychiatry, [5]Dept. of Mol. Physiol. and Biophysics, [6]Dept. of Intrnl. Med., Univ. of Iowa, Iowa City, IA; [7]Dept. of Neurosurg., Univ. of Iowa Hosp. & Clinics, Iowa City, IA; [8]Dept. of Neurosurg., Univ. of Iowa Stead Family Children's Hosp., Iowa City, IA

**Abstract:** The neural basis of breathing in the forebrain is an understudied research topic. Even though it is well-known that the spontaneous rhythm of breathing is controlled at the brainstem level, it receives inputs from the forebrain to modulate the spontaneous respiration according to the current behavioral needs (Rhone et al., 2020), for instance, during the production of speech, laughter, etc. Furthermore, the representation of respiration when breathing in different states of being awake, unresponsive under anesthesia, sleep, and breathing with ventilator support is not known. In this work, we address this issue by recording local field potentials (LFPs) from human epileptic patientsSimultaneous recording of LFPs and respiration signals from 8 patients (3 male, 5 female) with medically intractable epilepsy undergoing iEEG monitoring for seizure focus localization was made in 4 states: (i) spontaneous breathing in the awake state (ii) spontaneous breathing under anesthesia (iii) breathing with ventilator support (iv) spontaneous breathing during sleep. After de-noising the data, the correlation between inspiration peak locked averaged respiration and LFP was computed at each channel. Statistical significance was assessed using surrogate distribution from randomly aligned epoch averages. Changes in brain network across different states were assessed using block partial directed coherence at respiration frequency. The results across all subjects were summarized using linear mixed effects.Analysis of respiration signals showed a variance of inter-breathing-interval decreased from awake to sleep

to anesthesia. Computation of power spectral density showed a peak of power in the LFPs matching to respiration frequency in multiple brain areas including sensory, motor, and parietal across all states. Our findings indicate that temporal brain regions exhibit greater entrainment to breathing during the awake state, while parietal regions showed higher entrainment during anesthetized states. The amygdala and hippocampus exhibit entrainment to breathing during sleep, while motor areas exhibit entrainment across all states. Connectivity analysis revealed the middle frontal, orbital gyrus amygdala, and precentral gyrus to be hubs for respiration-related entrainment.To conclude, our data shows a wide forebrain network of brain areas is entrained by spontaneous respiration in all states of arousal. The behavioral, perceptual, and emotional consequences of this wide entrainment to respiration need to be investigated further.

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**Poster**

**PSTR033. Respiratory Control**

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**Program #/Poster #:** PSTR033.05/DD15

**Topic:** E.08. Respiratory Regulation

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NIH grant R01DA052953
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NIH grant R01NS113764

**Title:** Failure to breathe persists without air hunger or alarm following amygdala seizures

**Authors: *A. E. RHONE**[1], G. I. S. HARMATA[2], C. K. KOVACH[1], S. KUMAR[1], M. MOWLA[1], A. C. CHAN[3], G. B. RICHERSON[4], J. A. WEMMIE[3], B. J. DLOUHY[1];
[1]Neurosurg., [2]Neurosci. Grad. Program, [3]Psychiatry, [4]Neurol., Univ. of Iowa, Iowa City, IA

**Abstract:** Persistent apneas following the end of a seizure (postictal apnea) contribute to Sudden Unexpected Death in Epilepsy (SUDEP), the most common cause of death in intractable epilepsy. However, the neural mechanisms underlying postictal apnea are not known. The current study examines the neural basis of apnea that persists beyond the end of a seizure. 20 human subjects (age 3-59; 16 male, 4 female) were studied during intracranial electroencephalographic (iEEG) seizure monitoring. We evaluated respiratory outcomes from direct electrical stimulation to induce seizures and to functionally map the brain. SpO2, airflow, and chest wall motion were measured during stimulation mapping. Machine learning was used to

predict where apnea and persistent apnea were most likely to occur based on MNI coordinates of stimulated sites. To evaluate connectivity between the amygdala and brain regions not sampled with iEEG, one patient underwent electrical stimulation plus functional MRI (es-fMRI). In 18 subjects we observed apnea upon electrical stimulation of the amygdala or with seizure in amygdala. Sites outside the amygdala never elicited respiratory changes. In 5 subjects, apneas persisted beyond end of stimulation or stimulation-induced seizure. Subjects were unaware their breathing was disrupted, exhibited no air hunger, and showed no sign of distress. In some subjects, periods of apnea persisted for over 10 minutes. No changes in event related band power were observed during persistent apneas. Across subjects, machine learning identified a focal region of the amygdala where persistent apnea was most likely to occur. This area was within the previously described amygdala inhibition of respiration (AIR) site. Due to the persistence of apnea in the postictal or poststimulation period, we refer to this sub-site as the persistent amygdala inhibition of respiration (pAIR) site. Stimulation of the pAIR site concurrent with functional MRI resulted in BOLD signal changes in the pons, medulla and insula. Although a minority of subjects developed persistent apnea, those who did demonstrated no awareness of their apneas, even more than 10 minutes after stimulation or seizure end. Stimulation of the focal site which resulted in persistent apnea (pAIR site) altered BOLD in areas implicated in respiratory control and interoceptive processing. This suggests that some patients with medically intractable epilepsy may be more prone to developing postictal apnea, and a subregion of the amygdala is likely the locus of this effect. The pAIR site may be a future therapeutic target in the prevention of SUDEP.

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**Poster**

**PSTR033. Respiratory Control**

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**Program #/Poster #:** PSTR033.06/DD16

**Topic:** E.08. Respiratory Regulation

**Support:** NINDS K08 NS112573

**Title:** Causal connectivity of the amygdala inhibition of respiration (AIR) site to whole brain using concurrent electrical stimulation and fMRI (esfMRI)

**Authors: S. KUMAR**[1], H. OYA[1], A. E. RHONE[1], C. K. KOVACH[1], R. MOWLA[1], A. CHAN[2], J. WEMMIE[2], G. RICHERSON[3], *B. J. DLOUHY[4];
[1]Neurosurg., [2]Psychiatry, [3]Neurol., [4]Univ. of Iowa, Iowa City, IA

**Abstract:** Sudden unexpected death in epilepsy (SUDEP) is the most common cause of death in intractable epilepsy. Animal models and human studies suggest impaired breathing following

seizures as one of the leading causes of SUDEP. In our previous work (Dlouhy et al, 2015; PMID: 26180203), we identified a focal circumscribed site in the amygdala, referred to as the amygdala inhibition of respiration (AIR) site, stimulation of which either by spread of seizure or by electrical means causes cessation of respiration (apnea) without air hunger or alarm. The AIR site, therefore, is posited as a brain region that may mediate seizure-induced inhibition in SUDEP. However, the pathways via which the AIR site inhibits respiration are unknown. To determine these neural circuits in humans, we combined electrical stimulation of the AIR site while simultaneously acquiring whole brain fMRI BOLD signal to assess its causal influence on other brain areas. We conducted esfMRI in seven patients with intractable epilepsy undergoing intracranial EEG for seizure focus localization. Electrical stimulation (current range: 6-12mA, frequency: 100Hz) was applied in blocks of 30s, with a stimulation OFF block following every stimulation ON block in a 3T MRI scanner. Data was analyzed and summarized with a fixed effect analysis within the general linear modelling framework using SPM. Strikingly, AIR site stimulation caused reduced (negative) BOLD signal in the dorsal brainstem, thalamus, posterior cingulate and cerebellum. Although the significance of negative BOLD is debated, multiple studies suggest it represents suppression of neural activity. Thus, reduction of BOLD activity following AIR site stimulation suggests inhibition of sites in the pons and medulla, a region of the brainstem previously implicated in the control of breathing. We also found increased BOLD activity in ventral insula which is known to process interoceptive physiological changes in breathing, including air hunger. In conclusion, the AIR site has excitatory causal influence on a network of brain areas involved in representing and processing respiration. It exerts inhibitory causal influence on pontomedullary sites in the brainstem which may be the putative pathway via which respiration is inhibited in SUDEP.

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**Poster**

**PSTR033. Respiratory Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR033.07/DD17

**Topic:** E.08. Respiratory Regulation

**Support:** FAPESP proc. 2020/08620-1
FAPESP proc. 2022/15609-0
CNPq
CAPES-PROEX

**Title:** Selective activation of oxytocin signaling in the mouse respiratory parafacial region activates breathing

**Authors: *E. VERISSIMO DE ARAUJO**[1,2], P. E. SILVA[2], C. R. SOBRINHO[3], A. TAKAKURA[4], D. K. MULKEY[3], T. S. MOREIRA[2];

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**Abstract:** Selective activation of oxytocin signaling in the mouse respiratory parafacial region activates breathing.Emmanuel V. **Araújo**[1], Phelipe E. **Silva**[1], Cleyton R. **Sobrinho**[3], Ana C. **Takakura**[2], Daniel K. **Mulkey**[3], Thiago S. **Moreira**[1].[1]-Department of Physiology and Biophysics; Institute of Biomedical Sciences, University of Sao Paulo, São Paulo, Brazil.[2]-Department of Pharmacology; Institute of Biomedical Sciences, University of Sao Paulo, São Paulo, Brazil.[3]-Department of Physiology and Neurobiology; University of Connecticut, Connecticut, USA.
The neuropeptide oxytocin has been shown to stimulate breathing by activation of Gq coupled receptors that are widely expressed throughout the brain. Oxytocin is produced by neurons in the paraventricular nucleus of the hypothalamus (PVN) and recent evidence suggests oxytocin-expressing PVN neurons make monosynaptic projections to an important respiratory center called the ventral parafacial region (pF). Therefore, the goal of this study is to determine whether oxytocin modulates breathing at the level of the pF. Experiments were performed in urethane anesthetized wild type mice and mice that express channelrhodopsin-2/EYFP fusion protein in cre-recombinase dependent manner (Oxtcre$^{+/-}$, Ai32) maintained on a C57B6/J background. We used immunohistochemistry to show that oxytocin terminals are present throughout the ventral respiratory column, including the pre-Btzinger complex and ventromedial aspect of the pF region (pFV). We then performed pharmacological and optogenetic experiments to manipulate oxytocin signaling in the pFV while recording intercostal muscle activity ($int_{EMG}$) as an index of inspiration. We found that unilateral pFV microinjection of a selective agonist of oxytocin receptors (TGOT; 1 µM/30nL) increased $Int_{EMG}$ amplitude (16.3 ± 11.0 vs. saline: 2.7 ± 4.2%) and minute ventilation ($f_R$ x ampl) (17.4 ± 10.7 vs. saline: 4.3 ± 11%), without changing respiratory frequency (3.4 ± 12 vs. saline: -3.7 ± 6.6%). Similarly, unilateral optogenetic stimulation of oxytocin terminals in the pFV enhanced $Int_{EMG}$ amplitude (18.7 ± 8.3% of baseline) and minute ventilation (22.7 ± 5.8% from baseline), without changing respiratory frequency (3.65 ± 6.9% from baseline). These results suggest oxytocin signaling in the pFV increases breathing by preferentially stimulated tidal volume but not frequency. **Financial Support:** FAPESP, CNPq, CAPES-PROEX

**Disclosures:** **E. Verissimo de Araujo:** A. Employment/Salary (full or part-time); FAPESP. Other; CAPES-PROEX, CNPq. **P.E. Silva:** None. **C.R. Sobrinho:** None. **A. Takakura:** None. **D.K. Mulkey:** None. **T.S. Moreira:** None.

**Poster**

**PSTR033. Respiratory Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR033.08/DD18

**Topic:** E.08. Respiratory Regulation

**Support:** R01HL137094
R01HL104101

**Title:** Astrocyte Kir4.1 channels in the Retrotrapezoid nucleus contribute to the $CO_2/H^+$dependent drive to breathe

**Authors:** C. C. CLEARLY[1], J. L. BROWNING2[2], M. ARMBRUSTER[3], C. DULLA[3], M. L. OLSEN[2], ***D. MULKEY**[1];
[1]Physiol. and Neurobio., Univ. of Connectricut, Storrs, CT; [2]Virginia Tech. Undergraduate Neurosci. Program, Blacksburg, VA; [3]Tufts Univ., Boston, MA

**Abstract:** Chemosensitive neurons in the retrotrapezoid nucleus (RTN) regulate breathing in a $CO_2/H^+$-dependent manner. Astrocytes contribute to RTN chemoreception by providing a $CO_2/H^+$-dependent purinergic drive that enhances neural activity directly and indirectly by maintenance of vascular tone. Pharmacological evidence suggests that RTN astrocytes sense $CO_2/H^+$ by inhibition of Kir4.1/5.1 channels. This would result in reduced astrocyte $K^+$ buffering capacity allowing for the accumulation of $[K^+]o$ to further augment neural activity, a result we demonstrate here in RTN slices from WT mice. However, it remains unclear whether and how astrocyte Kir4.1 channels contribute to RTN chemoreception. Here, we generated an inducible astrocyte-specific Kir4.1 knockout (Kir4.1 cKO) by crossing $GFAP^{creERT2/+}$ mice with $Kir4.1^{f/f}$. We found that Kir4.1 cKO mice breathe normally under room air conditions but show a blunted ventilatory response to $CO_2$ ($p=0.0004$), which could be partly rescued by bilateral RTN injections of AAV5-gfaABC1D-eGFP-Kir4.1 overexpress Kir4.1 in RTN astrocytes. Further, bilateral injections of AAV5-Gfap-eGFP-iCre into the RTN of $Kir4.1^{f/f}$ mice to generate RTN astrocyte-specific Kir4.1 cKO mice, also blunted minute ventilatory response to $CO_2$ ($p=0.0025$). $CO_2/H^+$-inhibition of Kir4.1/5.1 has been shown to depolarize RTN astrocytes, a result we confirmed by expressing a genetically encoded voltage indicator AAV5-Gfap-eGFP-Archon1 in astrocytes. We found that ~75% of RTN astrocytes in slices from control mice are depolarized by $CO_2$, whereas only ~50% of RTN astrocytes in slices from Kir4.1 cKO mice respond to $CO_2$. We also found that $CO_2/H^+$-dependent purinergic drive to chemosensitive RTN neurons is reduced in Kir4.1 cKO mice, suggesting deletion of Kir4.1 from astrocytes disrupted the ability of these cells to release ATP in response to $CO_2/H^+$. These results support the possibility that astrocyte Kir4.1 channels contribute to RTN chemoreception.

**Disclosures: C.C. Clearly:** None. **J.L. Browning2:** None. **M. Armbruster:** None. **C. Dulla:** None. **M.L. Olsen:** None. **D. Mulkey:** None.

**Poster**

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**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR033.09/DD19

**Topic:** E.08. Respiratory Regulation

**Support:** NIH R01HL137094
NIH R01HL104101
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F31-HL156470

**Title:** $H^+$-dependent myo-inositol cotransport regulates activity of chemosensitve retrotrapezoid nucleus by KCNQ-dependent mechanism

**Authors:** J. SOTO-PEREZ, C. C. CLEARLY, ***C. R. SOBRINHO**, A. V. TZINGOUNIS, D. K. MULKEY;
Physiol. and Neurobio., Univ. of Connecticut, Storrs, CT

**Abstract:** KCNQ channels are a type of voltage-gated $K^+$ channel that activates at subthreshold potentials to regulate rest membrane potential and neural activity. The retrotrapezoid nucleus (RTN) is an important site of central respiratory chemoreception– the mechanism by which the brain regulates breathing in response to changes in tissue $CO_2$/pH– and previous and preliminary work showed that KCNQ2 (Kv7.2) channels regulate activity of chemosensitive RTN neurons. RNA sequencing results also suggest that RTN neurons express an $H^+$-dependent myo-inositol (myo) cotransporter (Slc2a13, HMIT) that is capable of importing myo to support production of phosphatidylinositol 4,5-bisphosphate (PIP2), a cofactor required for KCNQ2 channel activity. Based on this, we tested whether HMIT regulates activity of RTN neurons in a KCNQ-dependent manner. To examine this, we used slice-patch electrophysiology to determine the activity of RTN neurons during exposure to myo under control conditions and in the presence of high $CO_2$, when KCNQ channels are blocked with XE991 or when the PIP2 production was inhibited. For these experiments, chemosensitive RTN neurons were identified by location in the ventral parafacial region, their characteristic $CO_2$/$H^+$-sensitivity, and expression of the transcription factor Phox2b (a marker of RTN neurons) visualized using a cre-dependent *Phox2b* reporter mouse ($Phox2b^{cre}$::Ai14). We found that under control conditions (5% $CO_2$; pH 7.3) bath application of myo (5 mM) decreased activity of RTN chemoreceptors by average -0.8 ± 0.2 (p=0.0062). Consistent with the proton-dependent nature of HMIT, the inhibition during myo (5 mM) exposure under hypercapnic conditions (10% $CO_2$; pH 7.0) was potentiated ( -1.1 ± 0.2; p=0.0071). However, when PIP2 production was inhibited by UNC3230 (100nM), an inhibitor of a PIP5K1C necessary for the conversion of myo to PIP2, myo-dependent inhibition responses were blunted (-1.5 ± 0,5 control vs 0.2 ± 0.6; p= 0,0340). Further, when KCNQ channels were blocked with XE991 (10 μM) a subsequent exposure to myo presented a blunted response (0.9 ± 0.1 control vs 0.03 ± 0.09 XE991; p=0,0063). These results show that HMIT regulates activity of RTN neurons by a KCNQ-dependent mechanism that presumably involves rapid conversion of myo to PIP2 in close proximity to KCNQ channels.

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**Poster**

**PSTR033. Respiratory Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR033.10/DD20

**Topic:** F.03. Stress and the Brain

**Support:** KAKENHI22K06851

**Title:** Role of TRPV1 and TRPA1 on the pons of isolated brainstem-spinal cord preparation from neonatal rat

**Authors: *N. MASUTANI**[1], R. KAWABATA[2], Y. KOSAKA[1], K. KOGA[2], A. ARATA[1]; [1]Hyogo Med. Univ. , Dept. of Physiol., Nishinomiya, Japan; [2]Hyogo Med. Univ. , Dept. of Neurophysiol., Nishinomiya, Japan

**Abstract:** TRPA1 and TRPV1 are thermosensory TRP channels known to be mainly expressed in myelinated A-delta and unmyelinated C-fibers of peripheral nerves found in the spinal, vagus, and trigeminal nerve axons. The sensation of nociceptive spinal signals projects to the lateral parabrachial nucleus (LPB) of the pons via the dorsal horn, and LPB has also known as the system of inspiratory-expiratory (I-E) phase switching, which contributes to the control of respiratory rate. Thus, the tight interaction between respiration and pain signals as nociception-respiration coordination would be expected in LPB. However, the relationship between respiratory rhythm and pontine-level nociception has not been thoroughly investigated. In this study, we investigated the effects of TRPA1 and TRPV1 on the respiratory rhythm of pons-medulla-spinal cord preparations isolated from postnatal day 0-2 rats. Respiratory activity was recorded from the cervical fourth (C4) ventral nerve root. The TRPV1 channel receptor agonist facilitated respiratory rhythm, but TRPA1 agonists inhibited respiratory rhythm and reduced respiratory activity. These effects were shown for preparations with pons but not without pons. Optical imaging using voltage-sensitive dye detected the responded area of LPB from C8 dorsal root stimulation as a sensation input. A whole-cell patch clamp recorded The LPB neurons from the responded area. Non-respiratory neurons in the LPB received C8 dorsal root stimulation and showed a post-inhibitory rebound (PIR) when hyperpolarizing the current pulse by TRPV1. The LPB neurons increased firing rates and depolarized membrane potentials by TRPA1. Furthermore, we investigated whether TRPA1-induced suppression was involved in GABAergic inhibition. Since the GABAA antagonist bicuculline blocked respiratory depression, we realized that the GABAergic inhibitory system might mediate TRPA1 and have descending depression in response to nociception. These results suggested that 1) TRPV1 regulated that the non-respiratory LPB neurons, which expressed PIR, might be contributed to the onset-switching mechanism of the nociceptive-respiratory coordination network; 2) the analgesic effect of TRPA1 on respiration might be suppressed by excitation of the neurons in the LPB and the identity of this inhibitory system probably GABAergic neurons.

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**Poster**

**PSTR033. Respiratory Control**

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**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR033.11/DD21

**Topic:** E.07.a. Cellular properties – Interneurons and motor neurons

**Title:** A brainstem-spinal circuit critical for adaptive breathing

**Authors: *A. BREZINSKI**[1,2], H. SWEETMAN[1,2], K. SATKUNENDRARAJAH[1,2];
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**Abstract:** Cervical spinal cord injury (SCI) is a debilitating condition frequently leading to ventilatory complications, requiring mechanical ventilation, reduced quality of life, and increased mortality. Clinically, the hypercapnic ventilatory response is often used to evaluate a patient's readiness for weaning off mechanical ventilation. Therefore, it is essential to have a comprehensive understanding of ventilation and adaptive breathing in this context. While recent investigations into cervical excitatory interneurons (eIN) have demonstrated that these cells are essential for sustaining breathing following cervical SCI, the role of these neurons in the hypercapnic ventilatory response and other forms of adaptive breathing has yet to be investigated. Here we examine the role of cervical eINs in the hypercapnic ventilatory response as well as investigate the extent to which they are integrated into the respiratory network in both health and cervical SCI.
Using cellular-specific in vivo calcium imaging, we have established that populations of cervical eINs exhibit heightened activity in response to elevated carbon dioxide levels, suggesting their involvement in the hypercapnic ventilatory response. In line with this, chemogenetic silencing of cervical eINs in awake, freely moving animals revealed that these neurons are essential for the hypercapnic and hypoxic ventilatory response in uninjured states, but not so in cervical SCI, indicating an alteration in their function following injury. To investigate the connectivity of these interneurons, we employed retrograde monosynaptic rabies and transsynaptic pseudorabies viral techniques in transgenic mice expressing cre-recombinase in glutamatergic or serotonin neurons, respectively. This revealed connections between serotonergic neurons in the brainstem raphe nucleus and cervical eINs. Finally, we explored the modulation of this circuit to assess its potential for improving ventilatory function in response to respiratory challenges. These findings demonstrate a novel circuitry in respiratory plasticity and lay the groundwork for future therapeutic interventions targeting cervical eINs in respiratory disorders, including SCI.

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**Poster**

**PSTR033. Respiratory Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR033.12/DD22

**Topic:** E.08. Respiratory Regulation

**Support:** NIH F31-HL156470
NIH R01-HL137094

**Title:** Parafacial respiratory neurons contribute to breathing problems in KCNQ2 loss- and gain-of-function encephalopathy models

**Authors: *J. SOTO**, C. M. CLEARY, A. TZINGOUNIS, D. K. MULKEY;
Physiol. and Neurobio., Univ. of Connecticut, Storrs, CT

**Abstract:** Loss- and gain-of-function (GOF) mutations in KCNQ2 channels are a common cause of developmental and epileptic encephalopathy (DEE), a condition characterized by seizures, developmental delays, respiratory problems and early mortality. To understand how KCNQ2 dysfunction impacts behavior, we focus on control of breathing by Phox2b-expressing neurons in the retrotrapezoid nucleus (RTN) that function as respiratory chemoreceptors (regulate breathing in response to changes in CO2/H+). We found that Phox2b-expressing RTN neurons preferentially express Kcnq2 transcript and protein in the absence of other Kcnq isoforms. Based on this, we hypothesize that the RTN is vulnerable to dysfunction by KCNQ2 pathogenic variants. To test this, we used the cre-loxP system to conditionally delete Kcnq2 ($Phox2b^{Cre/+}$::$Kcnq2^{fl/fl}$) or express a DEE-associated Kcnq2 GOF variant ($Phox2b^{Cre/+}$::$Kcnq2^{R201C/+}$) in Phox2b neurons. Consistent with expectations, we found that deletion of *Kcnq2* from *Phox2b*-expressing cells increased baseline breathing, whereas expression of $Kcnq2^{R201C}$ in *Phox2b+* cells preferentially blunted the ventilatory response to CO2 during the light/inactive state when inhibition of KCNQ2 channels in RTN neurons by wake-on neurotransmitters is expected to be minimal. At the cellular level, CO2 sensitive RTN neurons expressing $Kcnq2^{R201C}$ exhibit decreased baseline activity and a blunted firing response to CO2. Further, bath application of a pan-KCNQ blocker (ML252; 10 uM) increased activity of RTN neurons in slices from control and $Phox2b^{Cre/+}$::$Kcnq2^{R201C/+}$ mice and negated differences between genotypes. These results represent the first evidence for a role of KCNQ2 channels in control of breathing, and identify RTN chemoreceptors as a likely basis for breathing problems in DEE.

**Disclosures: J. Soto:** None. **C.M. Cleary:** None. **A. Tzingounis:** None. **D.K. Mulkey:** None.

**Poster**

**PSTR033. Respiratory Control**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR033.13/DD23

**Topic:** E.08. Respiratory Regulation

**Support:** FAPESP
CNPq

**Title:** Neurons in the parafacial lateral region control the cardiovascular function of non-anesthetized rats.

**Authors: *K. S. MAGALHÃES**[1], M. P. DA SILVA[2], D. J. MORAES[3];
[1]Dept. of Physiol., Univ. of São Paulo, Ribeirão Preto, Brazil; [2]Dept. of Physiol. and Biophysics, Paulista Sch. of Medicine/Federal Univ. of São Paulo, Sao Paulo, Brazil; [3]Dept. of Biophysics, Inst. of Biomed. Sciences/University of São Paulo, Sao Paulo, Brazil

**Abstract:** The respiratory cycle at rest presents an active inspiratory phase, while expiration is a passive process. Active expiration is recruited under increased respiratory demand, resulting in an essential compensatory mechanism for increasing ventilation. Several studies have demonstrated that the lateral parafacial region (pFL) is important in generating active expiration and the simultaneous sympatho-excitation in response to increased respiratory demand, such as hypercapnia/acidosis and hypoxia. Besides, hypertensive animals present sympathetic overactivity and active expiration. However, the involvement of the pFL neurons in the control of cardiovascular function is still unknown. We hypothesized that the activation of pFL neurons increases the arterial pressure and heart rate of rats. Our aim was to evaluate the contribution of pFL neurons in the control of cardiovascular function of non-anesthetized rats. All protocols for Animal Experimentation were approved (#3/2019). The pFL neurons were activated by clozapine-N-oxide (CNO - 1mg/kg) after their transfection with an adeno-associated viral vector (AAV) to express the DREADDs - HM3D(Gq). Thirty days after the AAV injection, we recorded the diaphragm muscle activity and the pulsatile arterial pressure in non-anesthetized rats to evaluate the effects of pFL activation on the duration of inspiration (DI) and expiration (DE), respiratory frequency (fR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), and heart rate (HR). We recorded individual neurons in the pFL region expressing HM3D(Gq) to evaluate the effects of CNO on their electrical activity using whole-cell patch clamp recordings in acute medullary slices. Recordings in slices confirmed that the DREADDs ligand CNO excited the HM3D(Gq)-positive pFL neurons ($p<0.001$). Systemic injection (i.p.) of CNO decreased the DI ($0.14 \pm 0.01$ vs. $0.24 \pm 0.07$ s; $p = 0.004$), increased the DE ($0.25 \pm 0.03$ vs. $18 \pm 0.04$ s; $p = 0.001$) but did not affect the fR of rats expressing the HM3D(Gq) in the pFL region (n=5). Additionally, systemic injection of CNO increased SAP ($153.19 \pm 8.63$ vs. $130.18 \pm 11.05$ mmHg; $p < 0.0001$), DAP ($104.08 \pm 9.26$ vs. $86.78 \pm 8.89$ mmHg; $p < 0.0001$), MAP ($125.36 \pm 8.77$ vs. $105.87 \pm 9.55$; $p < 0.0001$), but did not affect the HR (n=6). On the other hand, systemic injection of CNO vehicle did not produce changes in rats expressing HM3D(Gq) in the pFL region (n=6). Moreover, systemic injection of CNO did not produce changes in rats that did not express the HM3D(Gq) in the pFL region (n=2). These data indicate that pFL neurons control the expiratory activity and the vascular function of non-anesthetized rats.

**Disclosures: K.S. Magalhães:** None. **M.P. da Silva:** None. **D.J. Moraes:** None.

**Poster**

**PSTR033. Respiratory Control**

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**Program #/Poster #:** PSTR033.14/DD24

**Topic:** E.08. Respiratory Regulation

**Support:** NIH F31HL160191
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NIH R01HL104101

**Title:** Investigation of thyrotropin-releasing hormone (TRH) neurons in the lateral hypothalamus

**Authors: *M. A. KHUU**, A. C. JACKSON, D. K. MULKEY;
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**Abstract:** The lateral hypothalamic area (LHA) is a subregion of the hypothalamus that is critical for the maintenance of many innate behaviors such as sleep/wake, arousal, metabolism, and stress/anxiety. These behaviors can be attributed to the diversity of cell types that are located within this region. One understudied LHA population is thyrotropin releasing hormone (TRH) neurons ($LHA^{TRH}$). In the paraventricular nucleus of the hypothalamus, TRH neurons are known to participate in the hypothalamic-pituitary-thyroid axis and TRH is released in response to decreased levels of thyroid hormone. In other areas, nonhypophysiotrophic TRH neurons have been shown to be a hypothalamic integrator of energy metabolism and are involved in behaviors such as arousal, respiration, and body temperature. Previous work has also indicated that exogenous *in vivo* microdialysis of TRH leads to prolonged stimulation of ventilatory output in rats. While the distribution of $LHA^{TRH}$ neurons has been previously reported, their downstream projection targets have been not been identified and their functional relevance at the cellular and whole animal level, particularly with regard to respiratory function, have not been probed. Here, we use a *Trh*-ires-cre mouse model to identify projection targets of $LHA^{TRH}$ neurons, characterize their intrinsic electrophysiological properties, and determine whether chemogenetic activation of this population may influence respiratory behavior. To identify projection targets of $LHA^{TRH}$ neurons, we made bilateral LHA injections of AAV-hSyn-DIO-mCherry in *Trh*-ires-$cre^{+/-}$ mice and in doing so identified labeled fibers in the dorsal septal nucleus, basolateral amygdala, the periaqueductal gray, and the nucleus tractus solitarius. Passive and active electrical properties were characterized in whole-cell current-clamp mode; most $LHA^{TRH}$ neurons exhibited tonic (32 out of 50 cells) and/or burst-like (36 out of 50 cells) firing properties, with a subset of neurons that exhibited spontaneous rhythmic bursting behavior (6 out of 50 cells). To determine the role of $LHA^{TRH}$ neurons in respiratory behavior, we chemogenetically activated the $LHA^{TRH}$ population and used whole body plethysmography to characterize baseline breathing under room air conditions following systemic injection of CNO (n=3). We found that activation of $LHA^{TRH}$ neurons had negligible effect on the depth, frequency, or pattern of respiratory activity. These results provide the first insight into projections and firing behavior of TRH neurons and suggest that $LHA^{TRH}$ neurons may not be directly involved in the control of breathing.

**Disclosures: M.A. Khuu:** None. **A.C. Jackson:** None. **D.K. Mulkey:** None.

**Poster**

**PSTR033. Respiratory Control**

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**Topic:** E.08. Respiratory Regulation

**Support:** IRB number: HSC-MS-20-1228

**Title:** Geometry in cortical breathing modulation networks

**Authors: *V. VASHIN**[1], B. TALAVERA[2], N. J. HUPP[2], O. MAGAÑA[2], S. LHATOO[2], N. LACUEY[2], Y. A. DABAGHIAN[2];
[2]Neurol., [1]Univ. of Texas Hlth. Sci. Center, Houston, Houston, TX

**Abstract:** In epilepsy, central apnea is strongly associated with Sudden Unexpected Death in Epilepsy (SUDEP), resulting in the deaths of approximately 7,000 persons with epilepsy each year in the USA and Europe alone. Currently, there are no neuromodulatory strategies for respiratory facilitation and apnea rescue that may prevent SUDEP. Thus, understanding the cortical breathing modulation networks will confirm the already known regions of respiratory control and identify other potential centers and help develop these strategies. We recorded stereotactic EEG in patients with epilepsy undergoing breathing tasks, constructed a functional network of their brain activity and analyzed the resulting dynamics. Specifically, we computed the Forman's curvature for each network—an analogue of the standard notion of curvature, adopted for discrete structures, such as datasets, networks and graphs. This measure enables a geometric view on data, e.g., it allows tracing the flow of information across the network, akin to liquid flow on curved surfaces. An important practical advantage of Forman's approach is its contextual flexibility: the effective geometry of the network can be defined through "weights" that empirically characterize the contribution of nodes and edges. Nodes with high absolute curvature are "hubs" of information represented by the selected weights; edges with high Forman-curvature dominate the information flow. To obtain complementary descriptions of the network dynamics, we used different measures for weighing the individual signals (e.g., entropy, power spectral density) and the couplings between signals (correlation, mutual information, power-time correlation). In particular, we found that different measures consistently highlight breath-controlling brain areas. Second, the precise dynamics of Forman-curvature evaluated for individual patients appears to capture the specifics of breathing dynamics at several timescales. These results provide novel insight into the neurophysiology of breathing modulation, and may enable targeted brain stimulation for the prevention of SUDEP.

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**Poster**

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**Title:** Syllable timing and shapes predicted by underlying breathing patterns in mouse ultrasonic vocalization

**Authors: *G.-H. LEE**[1,2], J. LEE[1], H. RHIM[1], J. CHOI[1];
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**Abstract:** Mouse ultrasonic vocalizations (USVs) exhibit a wide range of shapes and lengths, posing challenges in clustering the syllables into distinct groups. The underlying mechanism responsible for such variability remains unknown. However, recent studies have suggested an association between USV syllable length and breathing speed. In this study, we monitored the breathing patterns of adult male mice during interactions with females to explore the temporal relationship between breathing and USV production. We recorded two signals simultaneously: the local field potential (LFP) signal from the olfactory bulb (OB) and the temperature signal reflecting the direction of nasal airflow. Our findings reveal that the breathing pattern underlies both the timing and shape of USV syllables. Firstly, we analyzed the positioning of USV syllables within the breathing cycle and established a strong association between syllable length and the speed of breathing rhythm. For instance, faster breathing rhythm involved shorter vocalizations. In addition, the onset of syllables were phase-locked to a certain window within the breathing cycle, while longer syllables spanned a larger portion of the cycle. Interestingly, OB LFP signal and temperature signal exhibited distinct temporal profiles with respect to USV syllables. Secondly, to assess the extent to which variations in syllable shapes could be predicted from the underlying breathing pattern, we performed clustering analyses on OB LFP and breathing traces, grouping syllables occurring during specific breathing patterns. Although syllable shape cannot be deterministically predicted due to the inherent variation in various parameters, the information derived from the breathing pattern accounted for a significant portion of the variation in syllable frequency modulations. In conclusion, our study provides compelling evidence that the breathing pattern plays a pivotal role in determining the timing and shape of USV syllables in mice. Understanding the intricate relationship between breathing and vocalization may shed light on the underlying mechanisms of vocalizations in mammals.

**Disclosures: G. Lee:** None. **J. Lee:** None. **H. Rhim:** None. **J. Choi:** None.

**Poster**

**PSTR033. Respiratory Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR033.17/DD27

**Topic:** E.08. Respiratory Regulation

**Support:** Percival E. and Ethel Brown Foerderer Foundation Fellowship from Thomas Jefferson University
R01 HL161696
NIH OT2OD030534

**Title:** Dorsal motor nucleus of vagus neurons that project only to the heart contain unique biomarkers that represent a potential therapeutic target for heart conditions

**Authors: *C. ROSTAMI**[1], E. HORNUNG[2], R. VADIGEPALLI[2], J. S. SCHWABER[3]; [1]Thomas Jefferson Univ. Grad. Neurosci. Program, Philadelphia, PA; [3]DBI Functional Genomics/Computational Biol., [2]Thomas Jefferson Univ., Philadelphia, PA

**Abstract:** The dorsal motor nucleus of the vagus nerve (DMV), which provides parasympathetic innervation onto the intracardiac nervous system (ICN), has been shown to have a cardioprotective role following remote ischemic pre-conditioning (RIPC), which protects the organism from the pathological effects of myocardial infarction. However, the mechanism behind the DMV's cardioprotective effects is not well understood. Previous literature has shown that the DMV and the nucleus ambiguus (NA), another vagal motor nucleus, innervate different cell types within the ICN, and that DMV neurons project to many other organs in addition to the heart. In addition to the DMV cell bodies, the peptide Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP), which is believed to play a role in cardioprotection, has also been found to be expressed in the fibers innervating the ICN, where it is colocalized with the parasympathetic marker, ChAT. It is unknown whether these PACAP+ fibers originate from the DMV, from the NA, or from other ICN neurons. Since there has not been any organ-specific comparison done amongst DMV neurons, specificity of these biomarkers to cardiac-projecting DMV is unknown. We are working towards understanding the pathway of cardioprotection from the DMV to the ICN by identifying biomarkers of DMV neurons that project specifically to the ICN and biomarkers of DMV fibers distinguishable from other fibers at the level of the ICN. To identify cardiac-specific biomarkers within DMV, we are gathering and comparing transcriptomes of DMV neurons that project to the ICN to those of DMV neurons that project to other organs. We are also obtaining transcriptomic data from NA neurons that innervate the ICN, in order to distinguish DMV fibers from other fibers innervating the ICN. Our preliminary single-cell and spatial transcriptomic data has identified biomarkers of interest through analysis of relative gene expression differences between the DMV and the NA, as well as distinguishing cardiac-projecting DMV neurons versus DMV neurons that are not cardiac-projecting. Analysis of the datasets has identified two mRNA biomarkers of interest: *Adcyap1* and *Cartpt*, which are transcripts for the peptide PACAP and the protein CART, respectively. Recent research has suggested that one of the identified biomarkers, PACAP, plays a role in cardioprotection and our data has led us to hypothesize that these cardioprotective effects may arise from cardiac-projecting DMV neurons following RIPC. Testing the specificity of PACAP, and other biomarkers, to the DMV neurons that project only to the ICN, facilitates identification of potential targets for treatment of heart-related issues.

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**Poster**

**PSTR034. Sensorimotor Control of Action and Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR034.01/DD28

**Topic:** F.01. Neuroethology

**Support:** KQTD20200820113040070
JCYJ20200109141433384
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**Title:** A method for rating the level of consciousness during loss of consciousness induced by intravenous anesthetics in mice

**Authors: *C. PENG**[1], J. HU[2], X.-J. SONG[2];
[1]Southern Univ. of Sci. and technology, Shenzhen, China; [2]Southern Univ. of Sci. and Technol., Shenzhen, China

**Abstract:** Reversible loss of consciousness (LOC) induced by general anesthetics is a useful model for exploring the process of recovery of consciousness. Loss of the righting reflex (LORR) has been widely used to assess anesthetic state and evaluate LOC in animal experiments. We have recently observed that, at different periods of LORR, animals were able to respond at different levels to external stimuli, suggesting that the level of consciousness probably varied during LORR. We established a new rating scale for assessing the level of consciousness during LORR. This new method complemented use of LORR and helped to assess different levels of consciousness by measuring behavioral responses to external stimuli. We performed experiments in adult C57BL/6J mice and LORR was induced by intraperitoneal injection of propofol, pentobarbital or ketamine, separately. We observed and tested the following behavioral parameters, the spontaneous and cotton filaments evoked blinking reflex, response to noise (70 dB), olfactory response to unpleasant odor, response to mechanical stimulation on hind-paw plantar, somatic response to a given body position flip and spontaneous persistent tremor. Recordings began when the mice's righting reflex disappeared, the behavioral responses were recorded every 5 minutes, one point was assigned for a response and zero for no response. A stainless-steel, toothless alligator clip was also used to pinch the ventral skin surface between the footpad and the heel to test the pain response of mice during LORR. LORR began quickly after intraperitoneal injection of propofol, pentobarbital or ketamine. The scale scores decreased from a full score of 7 immediately after LORR to a score of 4-3 within 10-15 min, to a score ≤3 within 15-20 min, reaching bottom scores 0-2 within 25-35 min. We further defined the minimum responsive state (MRS) during LORR as an animal having an overall score ≤3 (0-3). Animals in the MRS, which lasted for about 45 min during the 15- to 60-min period after anesthetic injection, had the lowest level of consciousness and were unable to respond to external stimuli including the painful pinch. Some animals in the MRS could occasionally exhibit spontaneous limb, trunk or tail shaking. We tested the evoked responses and recorded the spontaneous behaviors of animals immediately after anesthetic application, throughout LORR, and to

recovery of the righting reflex (RRR). This new method complemented our use of LORR and helped to assess different levels of consciousness by measuring behavioral responses to external stimuli. This uniform scale helps to identify the shared molecular mechanisms under LOC induced by the diverse anesthetics.

**Disclosures: C. Peng:** None. **J. Hu:** None. **X. Song:** None.

**Poster**

**PSTR034. Sensorimotor Control of Action and Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR034.02/EE1

**Topic:** F.01. Neuroethology

**Support:** ONR MURI Grant N00014-19-1-2373

**Title:** Sensorymotor Processing of Chemotactile Stimuli in a Subepithelial Neuronal Network of Pleurobranchaea

**Authors: *J. CUI**[1,2,3], E. D. GRIBKOVA[1,3], T. NOREKIAN[4], R. GILLETTE[2,3];
[2]Neurosci. Program, [3]Coordinated Sci. Lab., [1]Univ. of Illinois at Urbana Champaign, Urbana, IL;
[4]Whitney Lab. for Marine Biosci., Univ. of Florida, St. Augustine, FL

**Abstract:** A neuronal subepithelial network (SeN) receives chemotactile sensation in the oral veil in the sea slug *Pleurobranchaea californica*. The SeN encodes two separate modes of sensation: (1) the first represents incentive and sums with excitation state in the feeding motor network as appetitive state, and (2) the second is an average of sensory stimulation across the oral veil, predicting the most likely source direction and acting as a motor template for the turn motor network in approach-avoidance responses. Our work tests the role of smaller axons of peripheral dopaminergic SeN neuron cell bodies in mediating incentive, and the role of larger axons with central cell bodies innervating the SeN in controlling the turn motor network responses. This network can be implemented in a computational model for motor control and attention.

**Disclosures: J. Cui:** None. **E.D. Gribkova:** None. **T. Norekian:** None. **R. Gillette:** None.

**Poster**

**PSTR034. Sensorimotor Control of Action and Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR034.03/EE2

**Topic:** F.01. Neuroethology

**Title:** Sensory feedback facilitates copulation in Drosophila males

**Authors: *M. WANG**[1], K. WANG[2], F. WANG[1];
[1]Chinese Acad. of Sci., Shanghai, China; [2]Lingang Lab., Shanghai, China

**Abstract:** Understanding how the sensory feedback modulates the motor actions is one major task in neuroscience. Here we focus on the sensory feedback in courtship process in *Drosophila melanogaster* males. The courtship ritual in males consists of a series of ordered behaviors that include orienting, tapping, singing, licking, attempting copulation and copulation. As the last step of the ritual, copulation is critical for the reproductive success. Successful execution of these motor actions requires integration of multiple sensory cues. By performing behavioral screening, we identified a group of sensory neurons which is essential for copulation. Ablating or silencing these neurons causes the failure of copulation, with no change in early courtship behaviors. Moreover, acute activation of these neurons induces copulation-like motor behavior. By using EM connectome and generating split lines, we are currently exploring the circuit mechanisms underlying this sensory feedback.

**Disclosures: M. Wang:** None. **K. Wang:** None. **F. Wang:** None.

**Poster**

**PSTR034. Sensorimotor Control of Action and Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR034.04/EE3

**Topic:** F.01. Neuroethology

**Support:** CIHR Grant PJT-166014
NSERC Grant RGPIN/05245
FRQNT Doctoral Scholarship
GRSNC Doctoral Scholarship

**Title:** An evolutionary perspective on decisions between and within cortical action circuits in mammals

**Authors: *P. CISEK**, A. NAKAHASHI;
Neurosci., Univ. of Montreal, Montreal, QC, Canada

**Abstract:** It has often been suggested that insights into brain organization may be found by considering its evolutionary history. Here, we use that approach to develop a hypothesis on the organization of mammalian circuits for selecting between and within different classes of actions. We begin with comparative work in early vertebrates suggesting that the pallial forebrain can be subdivided into a medial system for long-range exploration of the environment (hippocampal complex) and a ventrolateral system for interaction with the immediate environment. The latter

can be further subdivided into ventral, lateral, and dorsal pallial systems, which we suggest are involved, respectively, in identifying key stimuli, signaling interoceptive states, and detecting affordances in the environment. When our mammalian ancestors became nocturnal, the dorsal system (neocortex) was elaborated with stronger downstream projections and took on a major role in the control of distinct classes of actions. These included aspects of foraging such as searching, handling, and feeding, as well as defensive actions such as freezing or flight. We propose that each of these behavior types was guided by partially distinct "action maps" sensitive to the relevant affordances, each with a specific somatotopy of sensory input and motor output, as well as dedicated loops through the basal ganglia. We suggest that in modern mammals, the selection between different types of behavior (e.g. feeding vs. searching for food) takes place via selective invigoration from the basal ganglia through diffuse thalamocortical projections targeting a specific cortical action map. Once a type of behavior is chosen in this manner, the selection of a particular movement within that type (e.g. ingesting one piece of food vs. another) is made through competitive interactions within the activated action map. We propose that along the lineage from early mammals to primates, the action maps differentiated along with the expanding behavioral repertoire, particularly in the context of "handling" behaviors, giving rise to the complexity of primate fronto-parietal circuits. Our hypothesis makes a number of specific predictions about patterns of brain activation during natural behavior, some that are already supported by existing data and some that remain to be tested.

**Disclosures: P. Cisek:** None. **A. Nakahashi:** None.

**Poster**

**PSTR034. Sensorimotor Control of Action and Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR034.05/EE4

**Topic:** F.01. Neuroethology

**Support:** NIH 1DP2HD102042-01

**Title:** Probing mechanisms of caregiver recognition using social tadpoles

**Authors: *N. AKBARI**[1], J. BUTLER[2], L. A. O'CONNELL[2];
[1]Stanford Univ., San Francisco, CA; [2]Stanford Univ., Stanford, CA

**Abstract:** The ability of a neonate to use sensory cues to recognize caregivers from strangers is fundamental for survival. Some of our very first social interactions involve communicating hunger, avoiding dangerous stimuli, and interacting with siblings. Social recognition is also an important component of social decision-making, as infants must distinguish caregivers from strangers and display the appropriate behavior in a given social context. Despite the importance of the early stages of social cognition, it remains unclear how the developing brain processes sensory information to make context-appropriate decisions. *Ranitomeya imitator* tadpoles are excellent models of complex social behaviors as they display parental recognition and

communication of their needs using a robust motor display (e.g. begging) with high energy cost. We have discovered that olfactory cues are necessary and sufficient for caregiver recognition in *R. imitator* tadpoles. We show that *R. imitator* tadpoles differentially beg to their own species compared to a conspecific species (*Ranitomeya variabilis),* who place their predatory tadpoles into R. imitator pools. Tadpoles beg when presented with mom odors paired with a gray object, suggesting they will beg to any visual stimulus that smells like mom. In a series of experiments, we determine whether tadpole begging can increase towards non-caregiver cues by presenting tadpoles with a reward after exposure to a range of stimuli including an *R. variabilis* frog and *R. variabilis* odor paired with a custom-made robotic frog. We also explore *in vivo* imaging in *R. imitator* tadpole brains for decoding the neuronal circuits underlying olfactory recognition of caregiver by using calcium-sensitive dyes and multiphoton microscopy.

**Disclosures:** **N. Akbari:** None. **J. Butler:** None. **L.A. O'Connell:** None.

**Poster**

**PSTR034. Sensorimotor Control of Action and Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR034.06/EE5

**Topic:** F.01. Neuroethology

**Support:** KSN1823212

**Title:** Mechanical stimulation of the acupoint exerts analgesic effects via antagonizing of TRPV1 in carrageenan induced inflammatory pain mouse

**Authors: *S.-Y. KANG**[1], Y. RYU[2];
[1]Korea Inst. of Oriental Med., Daejeon, Korea, Republic of; [2]Dept Acupuncture, Meridian & Moxibustion, Korea Inst. Oriental Med., Daejeon, Korea, Republic of

**Abstract:** We have recently developed a mechanical acupuncture instrument (MAI), which applies mechanical stimulation to acupuncture points. Our previous studies have shown its effectiveness in treating hypertension and addiction in animal models. However, it remains unclear whether MAI has an analgesic effect on inflammatory pain. Thus, this experiment was designed to address two main objectives. First, we aimed to determine the optimal duration of MAI treatment at any given acupuncture point to achieve a better analgesic effect. Second, we aimed to investigate whether MAI treatment, or transient receptor potential vanilloid 1 (TRPV1) inhibition, would exhibit an analgesic effect and influence the expression of TRPV1 in the spinal cord as well as glial cells. We used the capsaicin test to identify the most effective acupoints and optimal treatment times for MAI. Additionally, we induced inflammatory pain in mice by administering a 2% carrageenan via intraplantar injection. To assess the analgesic effects of MAI treatment and TRPV1 inhibition, we evaluated pain-related behaviors using von Frey filaments and a thermal stimulator applied to the hind paw. In our study, we observed that applying MAI treatment for 60 seconds at the ST36 acupoint showed better analgesic effect compared to other

treatment conditions. Furthermore, this treatment demonstrated an analgesic effect in inflammatory pain-related behaviors. To investigate the involvement of TRPV1 in the analgesic effects, we administered capsazepine intrathecally, which reduced carrageenan-induced mechanical allodynia and thermal hyperalgesia. Additionally, we found that MAI treatment and capsazepine administration effectively suppressed the carrageenan-induced upregulation of TRPV1 and glial cells in the spinal cord. The findings from the present study provide evidence that the application of MAI at the ST36 acupoint effectively alleviated inflammatory pain behaviors and suppressed the activation of spinal TRPV1. These results strongly support the notion that MAI has the potential to serve as a valuable clinical therapy for the management of inflammatory pain.

**Disclosures: S. Kang:** None. **Y. Ryu:** None.

**Poster**

**PSTR034. Sensorimotor Control of Action and Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR034.07/EE6

**Topic:** F.01. Neuroethology

**Support:** Velux Stiftung Grant

**Title:** Development of a honey bee circadian neuron marker

**Authors: *M. A. GIANNONI GUZMAN**[1], O. H. COX[1], Z. C. SANCHEZ[1], M. ANDERSON[1], C. JOHNSON[1], D. G. MCMAHON[2];
[1]Vanderbilt Univ., Nashville, TN; [2]Dept of Biol. Sci., Vanderbilt Univ., NASHVILLE, TN

**Abstract:** Honey bees have been an important model for studying circadian rhythms for over a century. Yet very little is known about the neuroanatomy and inner workings of the bee's molecular clock. One of the main reasons for this has been the lack of tools to identify the circadian clock cells in vivo. To address this, we have developed the first of a series of tools to label the Pigment Dispersing Factor positive neurons in the bee brain. This tool drives GFP using the putative honey bee PDF promoter. Using primary cell cultures of pupal bee brains, we determined that our construct drives PDF specifically in PDF+ neurons with a 90% colocalization with the honey bee anti-PDF immunostaining. The addition of this tool will now allow us to study the properties of PDF neurons and their interactions with changes in circadian patterns and complex behaviors honey bees are known for.

**Disclosures: M.A. Giannoni Guzman:** None. **O.H. Cox:** None. **Z.C. Sanchez:** None. **M. Anderson:** None. **C. Johnson:** None. **D.G. McMahon:** None.

**Poster**

**PSTR034. Sensorimotor Control of Action and Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR034.08/EE7

**Topic:** F.01. Neuroethology

**Support:** Y Giraldo Startup Funds

**Title:** Visual and self-motion cues influence sun orientation in Drosophila melanogaster

**Authors: *H. PAE**[1], J. LIAO[2], Y. GIRALDO[2];
[1]Neurosci. Grad. Program, [2]Dept. of Entomology, Univ. of California, Riverside, RIVERSIDE, CA

**Abstract:** Orientation, movement with respect to an object, is a complex behavior many animals perform, integrating both external sensory cues and self-motion cues. Celestial cues, like the sun, allow animals such as *Drosophila* to orient in a stable direction for hours. A previous study tested *Drosophila* in a rigid tether arena where the fly cannot rotate and found that they orient to a sun stimulus and adopt individual headings that are maintained for hours. However, how visual and self-motion cues affect sun orientation has yet to be established in a rotating tether arena, where the fly can freely rotate around its yaw axis. To explore this behavior in the context of self-motion cues, we conducted 20-minute flight trials in the rotating tether arena. Like the rigid tether study, flies selected a heading relative to the sun and continued with their initial heading during the entire flight trial when the sun stimulus did not move. We found that 5 minutes is sufficient for a fly to select and maintain its heading as 76% of flies had less than a 45-degree difference between 5- and 20-minute headings. Unlike the previous sun orientation study in which flies were deprived of rotational cues, flies in our rotating tether arena adopted a new heading when the sun position shifted every 5 minutes. To examine how changes in visual stimuli and motor state impact heading direction, we tested flight behavior with various visual stimuli during flight or rest. Each experimental paradigm included a 5-minute sun orientation period, a 5-minute varied visual stimuli period, and a second 5-minute sun orientation period. The varied visual stimuli period was conducted under two different motor states, flight or rest. Regardless of the motor state or visual stimuli during the varied visual stimuli period, only moving the sun caused flies to select a new heading. To probe how long flies continued their heading when the sun did not move, flies were tested in a 5-minute flight trial, removed from the arena for 1, 2, 6, or 8 hours, and had a second 5-minute flight trial. We discovered that flies continued their initial heading for up to 6 hours but select new headings after 8 hours. Our findings show that when flies have rotational cues they can select and maintain a heading for up to 6 hours if the sun remains in the same position. However, this behavior is greatly affected by sun position change whereas other visual stimuli and motor states do not have large effects. Overall, our findings indicate that orientation is sensitive to specific changes in visual stimuli but not motor states, which lay a foundation to understand how the nervous system differentially processes sensory and motor cues during behavior.

**Disclosures: H. Pae:** None. **J. Liao:** None. **Y. Giraldo:** None.

**Poster**

**PSTR034. Sensorimotor Control of Action and Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR034.09/EE8

**Topic:** D.07. Visual Sensory-Motor Processing

**Title:** Large nesting behavior in deer mice is an inflexible habit that persists despite absolute visual deprivation: perspectives on compulsivity

**Authors: *H. MARX**[1], T. E. KRAHE[2], D. WOLMARANS[1];
[1]North-West Univ., Potchefstroom, South Africa; [2]Pontifical Catholic Univ. of Rio de Janeiro, Rio de Janeiro, Brazil

**Abstract:** Obsessive-compulsive disorder (OCD) is in some instances sensitive to external sensory feedback, an aspect that ensures optimal outcomes from psychotherapeutic interventions that are dependent on sensory stimuli, e.g. exposure-response prevention. Animal models of compulsive-like behavior are valuable tools that expand our understanding of repetitive, but seemingly goal-directed behaviors. Although several rodent models of behavioral persistence are described in literature, it remains difficult to elucidate the cognitive underpinnings of these phenotypes. In one such model, adult deer mice *(P. maniculatus bairdii)* of both sexes variably and spontaneously present with persistent and excessive large nesting behavior (LNB). However, it has not yet been determined if such behavior is dependent on visual feedback, which if true, could resemble a behavior akin to inflated goal-directed action-outcome processing. Here, we aimed to explore this question by employing 24 normal nesting (NNB) and 24 LNB-expressing mice (ethics no.: **NWU-00769-22-A5**). All mice were allowed to nest over one week to be classified as either NNB or LNB. Then, half of each group was reassessed under standard dark conditions (i.e. in the presence of low ambient light), while the other half was reassessed under conditions of absolute visual deprivation (VD; no ambient light). The following parameters were scored: i) total nesting score after one week, ii) nesting roundness and firmness, and iii) variance in terms between-day nesting performance. Our results show that LNB is persistent, consistent, and entirely dissociated from visual dependency ($p > 0.05$ for all comparisons of LNB behavior in ambient vs. VD conditions). In contrast, NNB varies significantly between testing days in both light conditions, with a greater degree of inconsistency shown under conditions of absolute VD ($p < 0.05$ for comparisons between NNB and LNB expression under conditions of VD). We conclude that LNB is a persistent behavioral habit, either learnt or innate, rather than a goal-directed behavior that is founded upon visually guided action-outcome processing. This is a vitally important finding, since it paves the way for investigations that seek to explore the naturalistic mechanisms that underlie habit-forming biobehavioral processes, which in turn, will elucidate our current views on the role of habit-proneness in the promulgation of compulsive symptoms.

**Disclosures: H. Marx:** None. **T.E. Krahe:** None. **D. Wolmarans:** None.

**Poster**

**PSTR034. Sensorimotor Control of Action and Behavior**

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**Program #/Poster #:** PSTR034.10/EE9

**Topic:** F.01. Neuroethology

**Support:** NIH Grant R35GM148349

**Title:** Nutrient-dependent sex differences in behavioral prioritization in C. elegans

**Authors: *C. BAINBRIDGE**[1], G. REILLY[1], J. WANG[3], D. S. PORTMAN[2];
[2]Dept. of Biomed. Genet., [1]Univ. of Rochester, Rochester, NY; [3]Univ. of Rochester Sch. of Med. and Dent., Rochester, NY

**Abstract:** To cope with nutrient deprivation, animals often reprioritize behaviors to favor feeding and rest over exploration. Because nutritional requirements and reproductive strategies differ by sex, this reprioritization can be sexually dimorphic. Work from our lab and others indicates that *C. elegans* exhibits sexually dimorphic behavioral and neuronal responses to nutrient availability. However, the mechanisms by which biological sex regulates neuronal function to produce sex-specific responses to nutrient status are poorly understood. In *C. elegans*, starvation and re-feeding provides a paradigm to understand how nutritional status and biological sex intersect to modulate behavioral state priority. Here, we investigate sex differences in behavioral priority by profiling distributions of locomotor states in fed and starved males and hermaphrodites. *C. elegans* exhibit stereotyped locomotor states (roaming, dwelling, and quiescence) that correspond to exploration, feeding, and sleep respectively. To observe these locomotor states, we recorded previously fed or starved adult *C. elegans* hermaphrodites and males on a high-quality bacterial food (HB101). From these recordings, we trained a Random Forest supervised machine learning model to identify these three states in both sexes. Our results indicate that male worms exhibit nutrient-dependent strategies distinct from hermaphrodites: males maintain exploration (roaming) and quiesce less than hermaphrodites even following substantial nutrient deprivation. To ask how biological sex may regulate nutrient-dependent locomotor states, we manipulated the genetic sex-determination pathway to sex-reverse specific tissues. These results suggest that the sexual states of both the nervous system and the intestine play a nutrient-dependent role in regulating locomotor state. To determine how nutritional status might be modulated by biological sex, we tested insulin and IGF signaling (IIS) pathway mutants for changes in nutrient-dependent locomotor behavior in both sexes. Preliminary results suggest that increased insulin signaling in males may promote sex-specific nutrient-dependent behavior. These studies will provide an opportunity to explore potentially conserved mechanisms by which genetic sex can regulate neuronal and behavioral responses to nutritional status.

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**Poster**

**PSTR034. Sensorimotor Control of Action and Behavior**

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**Program #/Poster #:** PSTR034.11/EE10

**Topic:** F.01. Neuroethology

**Support:** ANR-20-CE37-0015
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**Title:** Neuronal activity in prefrontal and ventral premotor cortex linked to social affiliative behaviors in free-moving macaques

**Authors: *J. BALDI**, E. DISARBOIS, G. COUDE, A. MENDEZ, L. MAIGRE, G. ANNICCHIARICO, M. CUVILLIEZ, J.-R. DUHAMEL, P. F. FERRARI;
Inst. of Cognitive Sci. Marc Jeannerod, Lyon, France

**Abstract:** Neurophysiological work has shown that neurons in premotor and prefrontal regions of macaque monkeys respond to motor action goals performed with different effectors (i.e. hand and mouth), as well as to social stimuli within the visual and acoustic domain. Notably, studies in macaques and marmoset have demonstrated that the behavioral context of heard vocalizations influences the neuronal activity in these regions. Historically, electrophysiological studies in nonhuman primates have involved the restraining of the animal, limiting its movements and therefore the repertoire of behaviors it could produce. This has been an evident obstacle to reliably studying the neural correlates of spontaneous, ecological behaviors, especially for physical and auditory social interactions. We built an experimental platform (EthoCage) involving a large enclosure in which we recorded wirelessly the neuronal activity of freely-moving macaques (alone or in pairs), while their behavior was tracked by a system of cameras and microphones. This experimental setup allowed us to acquire data on a wide range of ecologically-relevant behaviors.The first goal of this study was to investigate the neuronal activity in the ventral premotor cortex (F5) and in the dorsolateral prefrontal cortex (45a, 46v) during socially relevant spontaneous physical interactions between pairs of monkeys. We recorded from 128 channels chronically implanted in each of two individuals. The individuals were performing hand and mouth actions aimed at different social and non-social goals (i.e. allo-grooming, self-grooming, foraging).The second goal was to study in the same areas the encoding of auditory interactions. We recorded from individuals alone in the EthoCage, and played back vocalizations. For both social interaction modalities, we found interesting significant modulations of the single- and multi-unit activity in both regions. Preliminary data indicate that there is an encoding of the social context of motor actions, and that behavioral context affects the neural correlates of vocal exchanges. These finding highlight the importance of a new ecological approach to neuroscience in order to uncover new brain functions.

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**Poster**

**PSTR034. Sensorimotor Control of Action and Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR034.12/EE11

**Topic:** F.01. Neuroethology

**Title:** Neural circuits that regulate waking arousal in zebrafish

**Authors: J. M. PANLILIO**[1], D. C. BAZAN[1], *H. A. BURGESS[2];
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**Abstract:** Organisms alter their levels of arousal to match environmental cues. Heightened arousal is necessary to attend to important tasks, while reduced arousal is necessary for rest. The inability to appropriately modulate arousal is a symptom of several neurological disorders including schizophrenia, generalized anxiety, and depression. Neural circuits that control subtle changes in waking arousal that are environmentally driven are largely unknown. To address this, we have developed a behavioral paradigm in zebrafish where brief exposure to water flow results in a heightened but transient arousal state characterized by increased visual sensitivity and locomotor activity. To identify the neurons required for the movement component of arousal, we systematically ablated distinct neuronal populations by crossing Gal4 enhancer trap lines to UAS:nitroreductase. Ablation of neurons in the Gal4 y294 pattern - those present in the mesopontine tegmentum, rostral hypothalamus, dorsolateral hindbrain, habenula, and dorsal raphe - led to muted hyperactivity in response to the flow stimulus. Ablation of neurons just in the habenula or in the dorsal raphe did not result in any changes in the movement response to flow, suggesting these populations on their own are not necessary for this aspect of flow-induced arousal. To identify the relevant neurons, we performed whole brain neural activity labeling by performing fluorescent in situ hybridization for the early immediate gene *cfos*, and found that most brain regions are more active post-flow, with significantly elevated activity particularly in the lateral line ganglion, hypothalamus, and parts of the tegmentum. Finally, we identified potential neuromodulators involved in flow-induced arousal. Exposure to bromperidol and haloperidol (drugs that are known to block the dopamine 2 receptor) led to muted flow responses. However, knocking down all three zebrafish dopamine receptors (*drd2a*, *drd2b*, and *drd2l*) via CRISPR-Cas9 G0 injections did not alter the arousal response, suggesting these drugs may suppress the arousal response independent of dopamine signaling. Intriguingly though, exposure to bromperidol led to strong activation of a cluster of neurons in the mesopontine tegmentum that are spatially coincident with *adcyap1a* expressing y294-Gal4 neurons. Further investigation will determine which neuromodulators and neurons within the y294 pattern are involved in arousal modulation and which neuromodulators regulate arousal.

**Disclosures: J.M. Panlilio:** None. **D.C. Bazan:** None. **H.A. Burgess:** None.

**Poster**

**PSTR034. Sensorimotor Control of Action and Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR034.13/EE12

**Topic:** F.01. Neuroethology

**Support:** Wellcome 219627/Z/19/Z
Gatsby Charitable Foundation GAT3755

**Title:** Altered activity across the striatal-SC-PAG pathway following the learned suppression of escape

**Authors: *S. C. LENZI**[1], T. BRANCO[1], M. STEPHENSON-JONES[2], T. MARGRIE[1];
[1]Sainsbury Wellcome Centre, UCL, London, United Kingdom; [2]Sainsbury Wellcome Centre, UCL, london, United Kingdom

**Abstract:** Sensory stimuli that might signal threatening events are parsed by the brain to select behavioral responses that promote survival. Over the lifespan of an individual, however, constant revision of the threat value of stimuli in the environment is equally essential for optimizing behavioral selection (Evans et al. 2019). Recently we have described a new behavioral paradigm where laboratory mice learn to suppress their innate escape response to looming stimuli, in a stimulus-specific manner (LSE, Lenzi et al. 2022). Here we have investigated the neural mechanisms of LSE. We first recorded single unit activity in the midbrain and found that neurons involved in the execution of escape in both deep superior colliculus (SC) and dorsal periaqueductal gray (PAG) are less responsive to looming stimuli following LSE and that LSE leads to an upregulation of baseline activity in putative PAG inhibitory interneurons. To understand how this experience-dependent change in activity arises we then performed anatomical tracing experiments that revealed a putative disinhibitory pathway from the Tail of the Striatum (TS) to the SC/PAG via the SNr that we hypothesize could be involved in the experience-dependent regulation of escape. Pharmacological lesions of the TS and/or its dopaminergic input from the Substantia Nigra pars Lateralis (SNL) abolish normal escape behavior suggesting that this circuit could gate or otherwise modulate escape. Furthermore, both D1R- and D2R-expressing neurons in the TS showed reduced responses following LSE, indicating that they are modulated by escape experience. To evaluate whether the SNL could signal changes in threat intensity (Menegas et al. 2018) that may be used to update escape decisions, we next injected AAV5-TRE-GCaMP6f into the SNL of dopaminergic-neuron-specific tTA expressing (DAT-tTA) mice and recorded photometry signals from SNL dopaminergic axons in the TS. We observed reliable, large calcium responses to looming stimuli that correlated with stimulus saliency and escape probability. These calcium responses were reduced during and following LSE. Further, we found that recent threat escape experience, which occludes LSE, prevents attenuation of these SNL calcium signals recorded in the TS. We suggest that dopaminergic TS signals form part of the neuronal circuitry required for flexible escape behavior that is dependent on prior experience of threat. Further electrophysiology recordings, and optogenetic manipulations of glutamatergic inputs to the TS, particularly those arising from thalamus or cortex, will elucidate the mechanistic role of the SNL-TS circuit in the experience-dependent modulation of escape.

**Disclosures:** **S.C. Lenzi:** None. **T. Branco:** None. **M. Stephenson-Jones:** None. **T. Margrie:** None.

**Poster**

**PSTR034. Sensorimotor Control of Action and Behavior**

**Location:** WCC Halls A-C

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**Topic:** F.01. Neuroethology

**Support:** NIH R00NS109323
Whitehall Foundation

**Title:** The role of a human-specific gene, SRGAP2C, in modifying brain function and behavior

**Authors: *H. T. ZHAO**, A. MATTHIESEN, T. R. ANDERSON, K. K. GREEN, E. R. E. SCHMIDT;
Neurosci., Med. Univ. of South Carolina, Charleston, SC

**Abstract:** Humans have evolved a dramatic increase in cortical connectivity, which is thought to underlie our cognitive abilities; by contrast, impairments in cortical connectivity have been associated with neurodevelopmental disorders. However, how changes in cortical connectivity lead to enhanced or impaired learning and cognition remains poorly understood. Our previous work studying a human-specific gene duplication, *SRGAP2C*, showed that it mediates an increase in cortico-cortical connectivity; moreover, when expressed in mice, SRGAP2C improves sensory learning. Our current work seeks to investigate how SRGAP2C, as a human-specific modifier of cortical architecture, alters the circuit function underlying sensory processing and behavior. To achieve this, we perform *in vivo* wide-field calcium imaging of neuronal activity in SRGAP2C and wild-type (WT) mice both during passive sensory processing, and as they learn a sensory-based behavioral pipeline that tests multiple cognitive domains. This mesoscale approach, which enables access to the entire dorsal cortex, allows us to understand how neural dynamics propagate between cortical regions at specific time points during a behavioral task, including sensory processing, information integration, and motor planning and output.
Our results reveal distinct and widespread spatiotemporal neural dynamics in response to a sustained whisker stimulus that are altered in SRGAP2C mice as compared to WT controls, suggesting that the increase in long-range connectivity mediated by SRGAP2C modifies the temporal recruitment of cortical regions in response to sensory input. Furthermore, analysis of behavioral performance across our multi-phase behavioral pipeline suggests that specific cognitive domains involved in sensory learning, such as memory and cognitive flexibility, are differentially affected in SRGAP2C mice. By using SRGAP2C to investigate how modifying specific circuit motifs impacts neural dynamics and behavior, we provide insights into the unique role human-specific genes play in shaping the structure and function of cortical circuits.

**Disclosures:** **H.T. Zhao:** None. **A. Matthiesen:** None. **T.R. Anderson:** None. **K.K. Green:** None. **E.R.E. Schmidt:** None.

**Poster**

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**Location:** WCC Halls A-C

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**Topic:** F.01. Neuroethology

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1F32EY032776

**Title:** Investigations of population dynamics in the midbrain superior colliculus of the echolocating bat

**Authors: *G. SOMASEKHAR**[1], N. B. KOTHARI[2], C. F. MOSS[2], M. WOHLGEMUTH[1]; [1]Univ. of Arizona, Tucson, AZ; [2]Johns Hopkins Univ., Johns Hopkins Univ., Baltimore, MD

**Abstract:** Animals that exploit active sensing behaviors adjust motor behaviors to control sensory acquisition. These behaviors aid in the sampling of information across space and time. We investigated adaptive sensorimotor behaviors in echolocating bats performing naturalistic sonar tasks of navigation and target tracking. As the bats performed these tasks in the laboratory, we simultaneously recorded from populations of neurons in the midbrain superior colliculus (SC). We hypothesized that differences in SC population-level pre-motor signaling are driven by population-level sensory activation. To test this hypothesis, we employed a dynamical systems analysis technique to understand the relationship between changes in sensory and motor signaling in the population of recorded neurons. We analyzed windows of SC activity, beginning at echo arrival (sensory signal) until the onset of the subsequent sonar vocal-motor command to probe changes in population coding over time. Our results show that sensory processing and motor preparation phases have different neural state space trajectories, indicating a population level encoding of behavioral state. Furthermore, bats adjust in real-time their echolocation call rates and call patterns (sonar sound groups), based on immediate task demands. Strikingly, we were able to identify distinct neural state space trajectories, for each of these adjustments, indicating a population level encoding of real-time sensory acquisition requirements. This analytic approach can inform changes in population-level activity of neurons supporting adaptive sensorimotor behaviors. Future work will focus on how particular sensory states lead to distinct motor commands.

**Disclosures:** **G. Somasekhar:** None. **N.B. Kothari:** None. **C.F. Moss:** None. **M. Wohlgemuth:** None.

**Poster**

**PSTR034. Sensorimotor Control of Action and Behavior**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR034.16/EE16

**Topic:** F.01. Neuroethology

**Support:** NSF Award No. 1940957

**Title:** Investigating Direct and Indirect Basal Ganglia Pathways that Mediate Vocal Learning in Songbirds

**Authors: *M. NIGUDKAR**[1], A. JAGANNATHAN[1], S. W. BOTTJER[2];
[1]Dept. of Neurobio., [2]USC, USC, Los Angeles, CA

**Abstract:** Vocal learning in songbirds provides a powerful experimental model for motor skill learning, the acquisition of a stereotyped goal behavior through the refinement of variable actions. The cortico-basal ganglia pathways that mediate vocal learning in zebra finches (Taeniopygia guttata) are localized in two parallel circuits. These circuits traverse a cortical region (LMAN), a specialized region of the basal ganglia essential for vocal learning (Area X), and a region of dorso-medial thalamus (DLM). The output circuits of mammalian basal ganglia include a direct pathway that increases thalamic activity, as well as an indirect pathway that inhibits thalamic activity. This functional connectivity suggests that these pathways are involved in positive and negative reinforcement of behavior, respectively. Area X contains both striatal and pallidal neurons and includes projections that form functional analogs of mammalian direct and indirect pathways (Farries et al., 2005). Direct pallidal neurons of Area X send projections directly to DLM, whereas indirect pallidal neurons form intrinsic projections onto DLM-projecting neurons. We used tract-tracing techniques to label direct pallidal Area X→DLM projection neurons and immunohistochemical techniques to label neurons expressing the transcription factor FoxP2 (adult male zebra finches, n = 4). FoxP2 plays a critical role in human language development, with mutations leading to speech disorders such as childhood apraxia. Similarly, knockdown of the FoxP2 protein in Area X of juvenile songbirds impairs vocal learning. Based on previous research (Xiao et al., 2021), we predicted that direct neurons that send a projection to DLM would not express FoxP2. Our results support this hypothesis: DLM-projecting neurons in Area X never expressed FoxP2 (n = 467). We also observed a population of large pallidal-like neurons that did express FoxP2, but were not back-labeled from DLM. A marker of striatal neurons (DARPP-32) did not coexpress with FoxP2 in these large neurons, providing evidence that these putative indirect neurons are pallidal. Our findings offer FoxP2 as a possible marker for pallidal indirect neurons and support the existence of different subpopulations of neurons that likely correspond to direct and indirect pathways within Area X.

**Disclosures: M. Nigudkar:** None. **A. Jagannathan:** None. **S.W. Bottjer:** None.

**Poster**

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**Location:** WCC Halls A-C

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**Topic:** F.01. Neuroethology

**Support:** NIDCD Grant 1F31DC019307
NIH Grant 1R01DC018802

**Title:** Activity in mouse motor cortex reflects novel acoustic consequences of action

**Authors: *B. E. HOLEY**[1], D. M. SCHNEIDER[2];
[1]Ctr. For Neural Sci., NYU, New York, NY; [2]New York Univ., New York, NY

**Abstract:** Behavior is a strong predictor of sensory input. Movements with unexpected sensory consequences drive strong responses in primary sensory cortex that reflect a mismatch between experience - sensory input from the periphery - and expectation. The motor cortex is thought to be an important component of the cortex's prediction circuitry, specifically for its role in generating expectations via an internal model. However, it remains unknown whether or how motor cortical activity encodes the sensory consequences of movement or whether this encoding reflects expectation and experience. Here, we show that mouse motor cortex neurons are responsive to passive sounds, driven in part through long-range inputs from the auditory cortex. When a silent movement unexpectedly produces a sound, many individual motor cortical cells have rapid, sound-locked responses that cannot be accounted for by changes in behavior but instead can be accounted for by a model incorporating sound and movement responses. Through optogenetic tagging of auditory-projecting M2 cells, we find that activity evoked by the novel self-generated sound is relayed to auditory cortex, indicating that corollary discharge signals from motor cortex are not purely motor in nature. Interestingly, following several days of motor-sound coupling, motor cortical neurons become unresponsive to the same self-generated sound that previously drove a large response, suggesting a gating of responses to self-generated sounds based on expectation. Together, these findings reveal that the motor cortex transiently encodes the unexpected sensory consequences of a movement and reverts to stable, motor-centric dynamics once a sensory consequence becomes predictable, consistent with an important role for the motor cortex in the brain's prediction circuitry.

**Disclosures: B.E. Holey:** None. **D.M. Schneider:** None.

**Poster**

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**Topic:** F.01. Neuroethology

**Support:** NIH Grant 1R01-DC018802
NIH Grant T32-MH019524

**Title:** Prediction and Error in Mouse Auditory Cortex

**Authors: *N. AUDETTE**[1], D. M. SCHNEIDER[2];
[1]New York Univ. Ctr. For Neural Sci., New York, NY; [2]New York Univ., New York Univ., New York, NY

**Abstract:** Many of the sensations experienced by an organism are caused by their own actions, and accurately anticipating both the sensory features and timing of self-generated stimuli is crucial to a variety of behaviors. In the auditory cortex, neural responses to self-generated sounds exhibit frequency-specific suppression, suggesting that movement-based predictions may be implemented early in sensory processing. By training mice to make sound-generating forelimb movements, we recorded detailed neural responses while mice produced and experienced sounds that met or violated their expectations. We identified suppression of responses to self-generated sounds that was specific across multiple acoustic dimensions and to a precise position within the trained movement. Prediction-based suppression was concentrated in L2/3 and L5, where deviations from expectation also recruited a population of prediction-error neurons. Prediction error responses were short latency, stimulus-specific, and dependent on a learned sensory-motor expectation. Recording when expected sounds were omitted revealed expectation signals that were present across the cortical depth and peaked at the time of expected auditory feedback. Building on these findings, we are pursuing two new experimental directions. First, we are implementing simultaneous recordings from identified subregions of the auditory cortex and thalamus to understand how prediction signals traverse the distributed auditory circuit with millisecond resolution. Second, we are developing acoustic augmented reality home cage behaviors and freely moving recording techniques to understand how neural responses to a given external stimulus can shift dynamically to suit the needs of divergent behavioral contexts. Together, these experiments can identify circuit mechanisms that enable predictive processing across multiple interacting areas, and can provide insight into how these predictive processing circuits and other modes of contextual modulation are multiplexed across a fixed neural population.

**Disclosures: N. Audette:** None. **D.M. Schneider:** None.

**Poster**

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**Program #/Poster #:** PSTR034.19/EE19

**Topic:** F.01. Neuroethology

**Support:** NIH Grant 1R01-DC018802
NIH Grant 5T32NS086750-08

**Title:** A cortical role for skilled, sound-guided behavior in mice

**Authors: *G. ZEMPOLICH**, D. M. SCHNEIDER;
Ctr. for Neural Sci., New York Univ., New York, NY

**Abstract:** The abilities to detect errors and improve performance following mistakes are paramount to behaviors such as speech and musicianship. Although hearing is instrumental for monitoring and adapting these behaviors, the neural circuits that integrate motor, acoustic, and goal-related signals to detect errors and guide learning in mammals remain unidentified. Here, we show that the mouse auditory cortex encodes error- and learning-related signals during a skilled sound-generating behavior, and that auditory-cortical activity is necessary for learning from mistakes. We developed a closed-loop, sound-guided behavior that requires mice to use real-time acoustic feedback to guide their ongoing forelimb movements. Large-scale electrophysiology recordings from auditory cortex during behavior revealed that individual neurons encode rich information about sound, movement, and goal. Functional clusters of auditory cortex neurons signal errors and predict within-trial and across-trial changes in behavior. Brief, behavior-triggered optogenetic suppression of the auditory cortex hinders behavioral corrections on both rapid and long time scales, indicating that cortical error signals are necessary for learning. Together, these experiments identify a cortical role for detecting errors and learning from mistakes, and suggest that the auditory cortex may subserve skilled sound-generating behavior in mammals.

**Disclosures: G. Zempolich:** None. **D.M. Schneider:** None.

**Poster**

**PSTR034. Sensorimotor Control of Action and Behavior**

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**Program #/Poster #:** PSTR034.20/EE20

**Topic:** F.01. Neuroethology

**Support:** NIH Grant 1R01-DC018802

**Title:** Motor-sensory experience reshapes neural manifolds in auditory cortex to reflect acoustic expectations

**Authors: *W. ZHOU**[1], A. BALWANI[2], S. CHUNG[1,3], D. SCHNEIDER[1];
[1]New York Univ., New York, NY; [2]Georgia Inst. of Technol., Atlanta, GA; [3]Flatiron Inst. Ctr. for Computat. Neurosci., New York, NY

**Abstract:** Neural activity in auditory cortex (ACtx) is influenced by animal's motion expressed as a marked suppression of sound-evoked responses during movement compared to rest. This suppression of sound responses can be shaped by learning to reflect the acoustic features of self-generated sounds. This process, called predictive coding, is thought to involve the comparison between what an animal expects and what it hears. Yet it remains unknown how expectations are

represented in the ACtx; where expectation signals emerge with experience; nor how expectations alter the population dynamics of auditory cortical ensembles. Here, we show that ACtx is necessary for developing acoustic expectations; and that representation of auditory prediction emerge in ACtx and reshape population geometry following motor-sensory experience.We trained mice to push a lever to receive a water reward. Once mice mastered the lever behavior, we paired each lever press with a predictable tone and recorded in ACtx on the first and last days of experience with the sound-generating lever. We found that two thirds of ACtx neurons significantly changed their activity during movement hundreds of milliseconds prior to the self-generated tone, resulting in an overall ramping-up of baseline firing rates in ACtx. When averaged across all recorded neurons, movement-related changes were similar prior to and after motor-sensory experience. However, after motor-sensory experience movement-related activity became concentrated in neurons that are responsive to the expected tone frequency. Using a data driven matrix factorization approach, we found that these movement-related changes were concentrated in neurons with rapid but prolonged sound responses and is correlated with these neurons' relative tuning towards the expected frequency. PCA analyses showed that movement-related activity in ACtx was originally largely orthogonal to the neural dimension that encodes sound frequency; but this was altered by motor-sensory experience, resulting in a significant overlap in motor and acoustic dimensions, which is consistent with movement signals encoding an expectation for the paired sound. Predictive suppression, reallocation of movement signals, and reshaping of the cortical manifold could all be eliminated by selectively silencing the ACtx during motor-sensory experience. Together, these findings reveal that expectations about self-generated sounds emerge in ACtx, are encoded by movement-related activity, and reshape the population geometry of auditory cortex, which may facilitate predictive processing during behavior.

**Disclosures:** **W. Zhou:** None. **A. Balwani:** None. **S. Chung:** None. **D. Schneider:** None.

**Poster**

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**Program #/Poster #:** PSTR034.21/EE21

**Topic:** F.01. Neuroethology

**Support:** Leon Levy Fellowship in Neuroscience, Leon Levy Foundation
NIH Grant 1R01-DC018802

**Title:** Motor-related predictions in mouse auditory cortex are context-dependent

**Authors: *A. LA CHIOMA**, D. SCHNEIDER;
New York Univ., New York, NY

**Abstract:** Virtual reality (VR) has become an important tool in modern systems neuroscience, allowing researchers to couple experimentally controlled sensory feedback to an animal's real-

time behavior. Most VR systems yoke sensory feedback to an abstract measure of behavior (e.g. running speed) or to a contrived, non-natural behavior (e.g. operating a lever). Yet in nature, the consequences of one's action are often reproducibly coupled to specific behavioral kinematics (e.g. the moment one's foot hits the ground). Moreover, while many extant VR approaches focus on a single sensory modality, most natural behaviors have multimodal sensory consequences. Here, we developed a more naturalistic visual-acoustic VR system. We performed real-time locomotion tracking and gait kinematics analysis to provide artificial footstep sounds that were tightly yoked to a precise phase of the step cycle, creating an ethological and experimentally manipulable form of auditory reafference. While running on the treadmill and hearing footstep sounds, head-fixed mice repeatedly traversed two different contextual environments, each consisting of a distinct visual corridor accompanied by distinct footstep sounds. Using this system, we asked whether neural activity in the auditory cortex reflects predictions about the sound that footsteps are expected to produce, and whether prediction-related processing is modulated by context. Following behavioral acclimation, we made high-density neuronal recordings from primary auditory cortex as mice traversed the two VR environments and experienced either expected or deviant footsteps. We observed overall strong suppression of neural responses to self-generated sounds compared to the same sounds heard passively. We identified subsets of neurons that robustly showed a significant contextual modulation, responding differently to the same sound heard in the expected versus the unexpected context. These expectation violation-like signals emerge almost immediately after a mouse enters a new context, suggesting a rapid updating of predictions in parallel with behavior. We noted the presence of neurons with strong context-dependent modulation in infragranular cortex, consistent with other forms of predictive processing. Preliminary population-level analysis suggests that context information is embedded in auditory cortex population activity. Ongoing analyses are assessing how real-time footstep VR compares to more traditional speed-based VR systems. Overall, our results suggest that the auditory cortex combines auditory and motor signals with visual cues for flexible, context-dependent processing of self-generated sounds.

**Disclosures: A. La Chioma:** None. **D. Schneider:** None.

**Poster**

**PSTR034. Sensorimotor Control of Action and Behavior**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR034.22/EE22

**Topic:** F.01. Neuroethology

**Support:** New York Stem Cell Foundation

**Title:** Adaptive locomotor behavior on natural substrata via acoustic self-monitoring in mice

**Authors:** R. E. PETERSON[1], A. LA CHIOMA[2], J. GUEVARA[3], D. GARCIA[3], P.-N. BARTH[3], ***D. SCHNEIDER**[2];

[1]Ctr. for Neural Sci., New York Univ. Ctr. For Neural Sci., New York, NY; [3]Ctr. for Neural Sci., [2]New York Univ., New York, NY

**Abstract:** While moving on natural surfaces, mice produce broadcast sounds that alert potential predators to their location. Studies in wild mice show that mice actively adapt their locomotor behavior to minimize self-generated acoustic cues. Although laboratory mice are bred in captivity for generations, they retain innate predator avoidance behaviors such as preferring the periphery of an open arena and running for shelter in response to a looming visual cue. It remains unknown whether laboratory mice, like their wild counterparts, adjust their walking behavior on noisy surfaces to help avoid dangerous situations. Here, we made audio and video recordings of mice in a controlled laboratory setting as they walked on natural surfaces including sand, pebbles, and dry leaves. Different natural surfaces produce distinct sounds in frequency bands that are detectable by mouse predators. Deep quantification of open field behavior reveals that mice uniquely adapt their behavior on each surface. When a mouse's ears are plugged they behave as if they are on a quieter surface than they actually are, indicating the importance of acoustic self-monitoring for driving these surface-dependent behaviors. These experiments identify an innate behavior through which mice adjust their locomotion using acoustic self-monitoring, and which may facilitate predator avoidance.

**Disclosures: R.E. Peterson:** None. **A. La Chioma:** None. **J. Guevara:** None. **D. Garcia:** None. **P. Barth:** None. **D. Schneider:** None.

**Poster**

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**Topic:** F.01. Neuroethology

**Support:** H2020-MSCA-IF Grant 101026643
TUBITAK Grant 120E054

**Title:** Integration of visual and mechanosensory information in zebrafish during rheotaxis

**Authors: *O. KOC**, I. UYANIK;
Hacettepe Univ., Ankara, Turkey

**Abstract:** Animals construct a neural representation of their environment by combining sensory information captured by different sensory systems. The CNS is responsible for filtering, weighting, and integrating continuously captured signals to improve information processing, increase the reliability of perceived information, eliminate noise, etc. Our goal is to identify the dynamics of multisensory integration mechanisms that animals use to combine signals perceived by different sensory structures during their free behaviors. To achieve this, we built a swim tunnel to study multisensory integration during instinctive rheotaxis behavior of freely-swimming adult zebrafish, *Danio rerio*. Zebrafish perform rheotaxis by orienting their bodies

against the water flow to maintain their position without drifting in the flow. We place an obstacle in the water to obscure the flow, creating a local low-gradient regime for the fish to swim with less energy. When the obstacle is moved perpendicular to the water flow, the zebrafish senses these movements using their visual and mechanosensory systems and tracks the movement of the obstacle. Understanding the individual contributions of these sensory systems requires independent control of visual and mechanosensory cues presented to the fish. To implement this, we used a D-shaped cylindrical transparent tube attached to a linear actuator. The movement of this tube provides mechanosensory cues for the fish without creating any visual information. Inside this transparent tube, we placed a neon LED light strip attached to a different linear actuator. The independent movement of this light stripe provides visual cues without affecting the mechanosensory systems. We conducted multisensory conflict experiments with N=5 adult zebrafish to identify the filtering characteristics of the multisensory integration process in zebrafish. We estimated the frequency response to a sole mechanosensory, a sole visual, and a combined stimulus. Our results showed that mechanosensory stimulus trigger the tracking response of zebrafish. However, sole visual stimulus does not initiate movement. Nevertheless, the combined stimuli increase the performance of the fish as compared to mechanosensory only. This suggests that there is a nonlinear multisensory integration mechanism adopted by these fish. We are currently developing mathematical models to capture the characteristics of this process.

**Disclosures: O. Koc:** None. **I. Uyanik:** None.

**Poster**

**PSTR034. Sensorimotor Control of Action and Behavior**

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**Program #/Poster #:** PSTR034.24/EE24

**Topic:** F.01. Neuroethology

**Support:** H2020-MSCA-IF Grant 101026643

**Title:** Dynamic weighting of sensory weights in response to varying visual and electrosensory salience in weakly electric fish

**Authors: *A. DEMIREL**, I. UYANIK;
Hacettepe Univ., Ankara, Turkey

**Abstract:** Animals constantly combine information from multiple sensory systems to control their movement. This is performed by CNS via integrating information from multiple sensory modalities. In addition, animals dynamically adjust the contributions of each sensory modality to this process in order to increase their perceptual performance. Our objective is to demonstrate the relationship between the salience of the sensory information and the weights associated with various sensory systems. We designed and built an experimental setup to estimate the weights that weakly electric fish, *Eigenmannia virescens*, assigns to their visual and electrosensory

systems during refuge tracking behavior. In particular, we constructed a nested refuge structure, where we first have an inner transparent refuge connected to a linear actuator. This refuge is not visible to the fish, however, its movements stimulate the electrosensory receptors of the fish. We attached a second opaque white refuge encapsulating the transparent one and used another linear actuator to generate independent movement. This outer refuge is placed at a distance from the transparent refuge to solely generate visual stimulus without stimulating the electrosensory receptors. In that way, visual and electrosensory cues can be controlled independently. We 3D-printed three types of opaque refuges that have various window numbers to change the reliability of visual information. We modified the visual salience by changing the outer refuge in continuous experiments to observe the dynamic weighting of sensory modalities. Also, we changed the conductivity of the water (by adding a salt mix) continuously to observe the dynamic weighting when electrosensory salience is modulated. We experimented with N=4 fish under various sensory conditions to estimate the corresponding sensory weights. We observed that fish reacts to the changes in sensory salience by retuning its sensory weights. We are currently modeling this adaptation strategy to reveal the underlying mechanisms of dynamic reweighting during multisensory integration.

**Disclosures:** **A. Demirel:** None. **I. Uyanik:** None.

**Poster**

**PSTR034. Sensorimotor Control of Action and Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR034.25/EE25

**Topic:** F.01. Neuroethology

**Support:** TUBITAK Grant 120E198

**Title:** Modeling the Effects of Flow Speed on Smooth-Pursuit Tracking in Active Sensing Movements of Weakly Electric Fish

**Authors:** ***E. AYDIN**[1], I. UYANIK[2];
[1]Bioengineering Div., Hacettepe Univ., ANKARA, Turkey; [2]Dept. of Electrical and Electronics Engin., Hacettepe Univ., Ankara, Turkey

**Abstract:** Active sensing movements—additional motor actions to improve sensing— are employed by various organisms including weakly electric fish. The studies on understanding the mechanisms of active sensing behavior are gaining more interest due to biological implications and engineering applications. However, the studies on weakly electric fish exclusively focus on fish's response in a stationary environment. However, in their natural habitats, these fish experience varying flow speeds that possibly effect the active sensing movements used by these fish. This study presents a novel investigation into the effects of different flow speeds on the smooth pursuit tracking and active sensing movements of weakly electric fish, addressing the gap in the literature. To achieve this, we developed a special experimental setup that allows

weakly electric fish to engage in refuge-tracking behavior under controlled flow conditions. The experimental setup includes a refuge attached to a linear actuator, providing visual and electrosensory stimuli for the fish.We experimented with N=5 *Apteronotus albifron*s, with a complex stimulus movement profile consisting of a combination of 13 different frequencies ranging from 0 to 2 Hz. The experiments were repeated under various flow speeds (0-15 cm/s), illumination levels (light and dark), and refuge structures (with and without windows). Kinematic responses were recorded for five replicates under each sensory condition. In addition to the experiments, we conducted simulations using Matlab to further investigate the effects of flow speed. The analysis revealed that as flow speed increases, the tracking gain and phase lag of the fish decrease. Furthermore, active sensing movements were observed to increase in dark, which was consistent with the simulation results. The impact of increasing flow speeds on active sensing movements was found to be statistically significant ($p < 0.05$). Understanding the biological motivations behind active sensing movements is crucial for their application in engineering contexts. Therefore, studying these behaviors in the presence of water flow is of critical importance in understanding the natural motivations of active sensing in weakly electric fish.

**Disclosures:** **E. Aydin:** None. **I. Uyanik:** None.

**Poster**

**PSTR034. Sensorimotor Control of Action and Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR034.26/EE26

**Topic:** F.01. Neuroethology

**Support:** TUBITAK Grant 120E198
TUSEB Grant 16548
H2020-MSCA-IF Grant 101026643

**Title:** Active sensing as a part of multisensory behavioral control in weakly electric fish

**Authors: O. KARAGOZ**[1], A. KILIC[1], E. AYDIN[2], M. M. ANKARALI[1], *I. UYANIK[2];
[1]Middle East Tech. Univ., Ankara, Turkey; [2]Hacettepe Univ., Ankara, Turkey

**Abstract:** Multisensory behavioral control is a fundamental process in which the central nervous system combines and processes sensory signals from multiple sources, makes decisions based on perceived information, and generates motor actions to implement these decisions. This whole process works in a seamless closed-loop nature, where the dynamics of the sensory systems are tightly coupled with the dynamics of the locomotor systems. On the one hand, this coupling makes it quite challenging to analyze the sensory and motor systems during a multisensory behavioral control task. On the other hand, it enables animals to modulate the spatiotemporal features of the sensory information they receive from the environment using ancillary motor movements. These additional movements, termed active sensing movements, received

considerable attention from the neuroscience and engineering communities. However, a vast majority of the studies in the literature focus on the effects of active sensing on a single sensory channel. However, animals continuously combine available information from multiple sensory sources to improve their task-dependent perception. Therefore, it is essential to analyze active sensing within the context of a multisensory behavioral control task. In this work, we use a species of weakly electric fishes, Eigenmannia virescens, to reveal the underlying dynamics of active sensing movements during a multisensory behavioral task—the natural refuge tracking behavior. In their natural habitats, Eigenmannia prefers to hide within the tree trunks or other vegetative litter to shelter. Moreover, these fish track the moment-to-moment movements of their shelters by swimming forward and backward. During this amazing behavior, Eigenmannia continuously integrates information from their visual and electrosensory systems and generates ancillary active sensing movements to improve their perception. We developed a new experimental setup to analyze and model the role of active sensing movements during the multisensory refuge tracking the behavior of these fish. In simulation using the computational models of the actual fish, we showed that the proposed one-step ahead predictive uncertainty-based active sensing model outperforms the stochastic resonance generator and open-loop noise generator type models in terms of capturing the characteristics of the fish's refuge tracking response. In the near future, we plan to extend this model by directly fitting the input-output data from the fish to better explain the interaction between the multisensory integration and active sensing processes.

**Disclosures: O. Karagoz:** None. **A. Kilic:** None. **E. Aydin:** None. **M.M. Ankarali:** None. **I. Uyanik:** None.

**Poster**

**PSTR034. Sensorimotor Control of Action and Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR034.27/EE27

**Topic:** F.01. Neuroethology

**Support:** TUBITAK Grant 120E198

**Title:** Predictive state-estimation uncertainty drives task-dependent active sensing

**Authors: *A. KILIC**[1], O. KARAGOZ[1], E. AYDIN[2], M. M. ANKARALI[1], I. UYANIK[2]; [1]Electrical and Electronics Engin., Middle East Tech. Univ., Ankara, Turkey; [2]Hacettepe Univ., Ankara, Turkey

**Abstract:** The sensory and motor systems in animals are linked: the central nervous system generates motor actions using sensory feedback, while motor movements, in turn, shape the sensory information. Animals benefit from this inevitable phenomenon by producing ancillary active sensing movements to improve the sensory feedback they receive from the environment. Despite the ubiquitous nature of this behavior across taxa, the underlying mechanism of active

sensing is not yet fully understood.This study aims to identify the behavioral mechanisms of active sensing movements performed by a species of weakly electric fish, Eigenmannia virescens. These fish live in small shelters in the water to avoid predators in their natural habitat. Moreover, they tend to follow their refuge if it is in motion. We developed an experimental setup to mimic the natural behaviors of the fish in the laboratory. A PVC refuge, whose movement can be controlled by a motion control system, stimulates the fish's refuge tracking response. In light, Eigenmannia virescens quite accurately tracks the movements of the refuge using feedback from their visual and electrosensory systems. However, while performing this behavior in the dark, fish exhibit high-frequency movements in addition to their regular tracking response. We hypothesize that this high-frequency movement generated by the fish is an active sensing movement to increase the state estimation performance.To test our hypothesis, we created a musculoskeletal and sensory model of the fish in a simulation environment. In addition, we developed a state estimator based on Extended Kalman Filter to model the sensory perception of the fish. Different from the recent works, we modeled the active sensing generator as a closed-loop system, which produces ancillary active sensing movements based on the predictive uncertainty of the stochastic closed-loop system model. This closed-loop process aims to choose the optimal active sensing action, which minimizes the predictive uncertainty of the subsequent movement. In our model---as in the literature---, active sensing inputs act as a disturbance to the behavioral controller. Thus, the optimization routine weighs both the state-estimation performance and the energetic cost of input. We validated the performance of our model using actual refuge tracking data from N=3 fish. We used leave-one-out cross-validation over ten replicates for statistical evaluation of our results. Our results showed that the proposed active sensing generator produces refuge-tracking responses within the actual fish's trial-to-trial variability range.

**Disclosures:** **A. Kilic:** None. **O. Karagoz:** None. **E. Aydin:** None. **M.M. Ankarali:** None. **I. Uyanik:** None.

**Poster**

**PSTR035. Stress and Neuroimmunology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR035.01/EE28

**Topic:** F.03. Stress and the Brain

**Support:** PC-164-23

**Title:** Impact of social isolation stress on stress-related behaviors, neuroinflammation, and locus coeruleus function

**Authors: S. O. OGUNSANMI**, *J. A. TKACZYNSKI, A. J. K. REED, D. J. CHANDLER; Cell Biol. and Neurosci., Rowan Univ., Stratford, NJ

**Abstract:** Social isolation, the state of prolonged absence of social contact or meaningful social interactions, has been recognized as a significant stressor that can impact various aspects of an individual's well-being and is a risk factor for the development of mood disorders. Studies examining the impact of social isolation have demonstrated alterations in both structural and functional changes in the brain. During the COVID-19 pandemic, widespread social isolation was a significant stressor on the global population. Thus, clarifying how social isolation impacts the brain is a necessary step in reducing the burden that the pandemic will impose on public mental health. In this set of studies, we aim to clarify how chronic social isolation stress affects the function of and neuroinflammation in the noradrenergic nucleus locus coeruleus (LC), a bilateral brainstem structure that provides noradrenergic tone to the central nervous system whose activity is tightly correlated with indices of behavioral arousal. Prior observations from our laboratory show that different stressors increase anxiety-like behavior, alter LC physiological properties, and increase penetrance of LC by activated pro-inflammatory microglia. Here we show that social isolation stress selectively increases freezing behavior in the open field in female, but not male rats, and the adoption of a passive coping strategy in the defensive shock probe burial task in males. We aim to further clarify the relationship between social isolation stress and anxiety-like and stress coping behavior, and determine the effects of social isolation stress on LC physiology and neuroinflammation throughout the brain.

**Disclosures: S.O. Ogunsanmi:** None. **J.A. Tkaczynski:** None. **A.J.K. Reed:** None. **D.J. Chandler:** None.

**Poster**

**PSTR035. Stress and Neuroimmunology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR035.02/FF1

**Topic:** F.03. Stress and the Brain

**Support:** K01 MH117343
Tulane Start-up Funds

**Title:** Acute stressor exposure effects on central and systemic B lymphocyte profiles in young adult male and female mice

**Authors:** M. MARCUS[1,2], I. PURSELL, BS[1], R. FREITAS[1], L. GARFINKEL[1], C. PORRETTA[1], H. WANG[1], S. RAWLINS[1], ***E. ENGLER-CHIURAZZI**[1];
[1]Tulane Univ., New Orleans, LA; [2]Univ. of Manchester, Manchester, United Kingdom

**Abstract:** While a role for T lymphocytes in the stress response is well-documented, appreciation for the involvement of B cells has been historically understudied. Importantly, emerging evidence suggests that B cell profiles are fundamentally shifted in the context of stress and that animals deficient in B cells show susceptible phenotypes. We aimed to characterize B cell profiles following a single psychological stress exposure. We hypothesized there would be

time-point and tissue-specific differences in B lymphocyte expression following stress exposure. Specifically, we anticipated that acute stress would induce general lymphopenia that would recover as time since stress exposure increased, while some subsets of B cells (e.g. plasma cells) would be elevated. 3-month-old male and female C57BL/6J mice experienced either 6hrs of restraint or 12-14hrs of social isolation; control mice remained group-housed in their home cages. One-way ANOVA followed by multiple comparisons of flow cytometry data (percent parent population) discerned B cell subsets in blood, spleen and brain among mice whose tissues were collected day of stress, 4 days (4D) or 7 days (7D) post-stress (N=10/group). We observed stressor, tissue, and time-specific effects, distinct to the stress paradigm. For restraint-exposed mice, there were no differences in B cells in any tissue initially. B cells were higher in spleen ($p$=0.005), blood ($p$<0.001) and brain ($p$<0.001) 4D post-stress. The increase in B cells in the brain may be driven by B1a cells ($p$<0.05). Interestingly, males exhibited elevated B1a cells at 4D while females showed elevated B1a cells at 7D. The T:B ratio was lower in blood at 4D ($p$<0.05) and 7D ($p$<0.05) post-restraint-stress compared to non-restrained mice, whereas the T:B ratio decreased at 4D post-stress ($p$=0.005) in the brain and at 7D post-stress ($p$<0.01) in the spleen. Following social isolation, B cell counts were initially reduced in blood ($p$<0.005) and brain *(*$p$<0.05). B cell counts in spleen were decreased only 7D post-stress ($p$<0.05). Interestingly, B1a cell counts were not altered in any tissue at any timepoint. The T:B ratio initially increased in both blood (p<0.005) and brain ($p$<0.05) before returning to baseline. Spleen showed no T:B ratio changes. These findings demonstrate that B cell profiles in distinct tissues respond differently to stress and show that varying types of psychosocial stress elicit different responses. Future work is needed to understand the functional significance of B cell changes post-stress.

**Disclosures:** **M. Marcus:** None. **I. Pursell:** None. **R. Freitas:** None. **L. Garfinkel:** None. **C. Porretta:** None. **H. Wang:** None. **S. Rawlins:** None. **E. Engler-Chiurazzi:** None.

**Poster**

**PSTR035. Stress and Neuroimmunology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR035.03/FF2

**Topic:** F.03. Stress and the Brain

**Support:** NRF Grant 2021R1A2C2014123
NRF Grant 2018M3C7A1024150

**Title:** Single-cell trancriptome analysis uncovers chronic stressed-induced BBB leakage and immune cell infiltration in the mouse brain

**Authors: *S. SHIN**, J. LEE, J. KWON, K. CHOI, H. KANG;
Chung Ang Univ., Seoul, Korea, Republic of

**Abstract:** Exposure to chronic stress can contribute to major depressive disorder. To mimic several aspects of depression, the chronic unpredictable stress (CUS) mouse model is extensively used. Increasing evidence suggests that quantitative changes in several cell types related to the blood-brain barrier (BBB) and neuroinflammation are associated with depressive behavior. However, a complete catalog of the heterogeneous cell types found within the CUS mouse brain is lacking and the underlying mechanisms of stress-induced depression remain elusive. Here, we used single-cell transcriptomics to examine approximately ~96,000 cells from the whole brain of CUS mice (n=4) and controls (n=4). We identified 20 broad cell types and 47 molecular clusters. Among 20 cell types, endothelial cells and pericytes were significantly decreased in the CUS mouse brain. Conversely, T cells and B cells were increased. The functional annotation of differentially expressed genes enriched in immune activation and immune cell migration along with endothelial cell dysfunction. We present evidence that stress-induced neuroimmune activation could be associated with BBB breakdown. Collectively, this study provides a comprehensive single-cell atlas of the CUS mouse brain and molecular foundation for investigating cell type-specific responses to chronic stress.

**Disclosures: S. Shin:** None. **J. Lee:** None. **J. Kwon:** None. **K. Choi:** None. **H. Kang:** None.

**Poster**

**PSTR035. Stress and Neuroimmunology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR035.04/FF3

**Topic:** F.03. Stress and the Brain

**Support:** ORWH-U54-MH118919

**Title:** Defining the relationship of elements crossing between the nucleus of the solitary tract and the area postrema.

**Authors: *E. A. CASTELLANOS**[1], J. A. SHENG[1], S. A. TOBET[2,1,3,4];
[1]Biomed. Sci., [2]Biomed. Engin., Colorado State Univ., Fort Collins, CO; [3]Dept. of Psychiatry, [4]Innovation Ctr. on Sex Differences in Med., Harvard Med. Sch., Boston, MA

**Abstract:** Maternal immune activation during fetal development is a potential risk factor for neuropsychiatric disorders in adulthood. Addition stressful events later in life have been associated with the onset of neuropsychiatric conditions. One signature of stressful events in the nervous system may be changes in microglial remodeling, particularly in brain regions linked to autonomic circuits. In mouse models of maternal immune activation, the inflammatory response can be initiated by activating a range of different toll-like receptors (TLRs). In the current study, we utilized the TLR7 agonist resiquimod as a pro-inflammatory initiator to mimic a viral infection. On gestation day (G) 12.5, we administered resiquimod (2.0 mg/kg) to timed pregnant mice. On postnatal day (P) 21, the offspring from these dams were subjected to acute restraint stress for 20 minutes, followed by a recovery period of 60 minutes. Afterward, the offspring

were transcardially perfused with 4% paraformaldehyde, and the brainstems were subsequently extracted for immunolabeling with ionized calcium binding adhesion molecule-1 (IBA-1) to identify microglia, as well as calcitonin gene-related peptide (CGRP), a potent vasodilator. The objective of this study is to determine the distribution of microglia and CGRP across the nucleus of the solitary tract (NTS) from its rostral to caudal aspects and investigate how this distribution changes after stress in juvenile mice. Microglia exhibited a higher density in the area postrema adjacent to the caudal NTS, along with larger microglial morphologies. Immunoreactive CGRP fibers were observed lining the area postrema adjacent to the NTS, and maternal immune activation resulted in reduced CGRP levels in both restraint and nonrestraint groups. These findings suggest differences along the area postrema-NTS border that may impact NTS neuronal perception of vagal nerve stimuli. As the area postrema is a circumventricular organ with fenestrated capillaries, it may be particularly interesting to examine the interactions between these adjacent regions with differential blood brain barrier function. This study adds to the characterization of the NTS chemoarchitecture in our lab and begins to tease out potential effects of stressful challenges during the lifespan.

**Disclosures: E.A. Castellanos:** None. **J.A. Sheng:** None. **S.A. Tobet:** None.

**Poster**

**PSTR035. Stress and Neuroimmunology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR035.05/FF4

**Topic:** F.03. Stress and the Brain

**Title:** Blood-based Biomarkers for Intestinal Permeability: A Pilot Study of US Veterans with and without Posttraumatic Stress Disorder

**Authors: *C. E. STAMPER**[1,2,4], A. J. HOISINGTON[1,5,4,2], K. A. STEARNS-YODER[1,4,2], F. HAGHIGHI[6,7], C. A. LOWRY[8,9,10,4,2], L. A. BRENNER[1,3,4,2];
[1]MIRECC, Rocky Mountain Regional VA Med. Ctr., Aurora, CO; [2]Physical Med. and Rehabil., [3]Departments of Psychiatry and Neurol., Univ. of Colorado Sch. of Med., Aurora, CO; [4]Military and Veteran Microbiome: Consortium for Res. and Educ. (MVM-CoRE), Aurora, CO; [5]Dept. of Systems Engin. and Mgmt., Air Force Inst. of Technol., Wright-Patterson AFB, OH; [6]Icahn Sch. of Med. at Mount Sinai, New York City, NY; [7]James J. Peters Veteran Affairs Med. Ctr., New York City, NY; [8]Dept. of Integrative Physiol., [9]Ctr. for Neurosci., Univ. of Colorado Boulder, Boulder, CO; [10]Ctr. for Neurosci., Univ. of Colorado Anschutz Med. Campus, Aurora, CO

**Abstract:** While many studies of intestinal permeability (IP) are focused on those with gastrointestinal (GI) disorders, there is a rising trend to analyze IP among individuals with mental health (MH) conditions, including posttraumatic stress disorder (PTSD), with/without diagnosed GI conditions. This interest stems from the association between gut dysbiosis and chronic inflammation, mechanisms linked to stress-related somatic and MH conditions. Efforts have resulted in exploration of non-invasive and feasible measures to identify an IP biomarker

that could also serve as a treatment target. Additionally, those conducting studies regarding IP often recruit relatively healthy individuals without acute/chronic health problems and compare the levels to those obtained from participants with conditions of interest. This study aimed to assess correlations between IP blood-based biomarkers, as well as examine associations between blood-based biomarkers of IP and MH symptoms. Blood was sampled from seventeen military Veterans with variable severity of PTSD symptoms per the Posttraumatic Checklist for DSM-5, and analyzed blood biomarkers of IP including citrulline, diamine oxidase, glucagon-like peptide-2, intestinal fatty-acid binding protein, lipopolysaccharide binding protein, lipopolysaccharide, and zonulin. Correlations between the IP blood-based biomarkers ranged from of -0.31 to 0.35 (Spearman test for correlation coefficient). None of the measured biomarkers were significantly correlated to PTSD symptom severity scores (-0.34 to 0.05; Spearman test for correlation coefficient). Our results call into question the specificity of blood-based biomarkers of IP when: (1) studying persons with/without PTSD symptoms in whom clinical GI disorders are not necessarily the focus of the scientific endeavor; and (2) comparing IP results among individuals with more characterized disease states to those without the disease. Studies are needed to explore the role of external factors on IP and to determine if the biomarkers studied are appropriate for measuring IP in people with a range of symptoms related to PTSD.

**Disclosures: C.E. Stamper:** None. **A.J. Hoisington:** None. **K.A. Stearns-Yoder:** None. **F. Haghighi:** None. **C.A. Lowry:** None. **L.A. Brenner:** None.

**Poster**

**PSTR035. Stress and Neuroimmunology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR035.06/FF5

**Topic:** F.03. Stress and the Brain

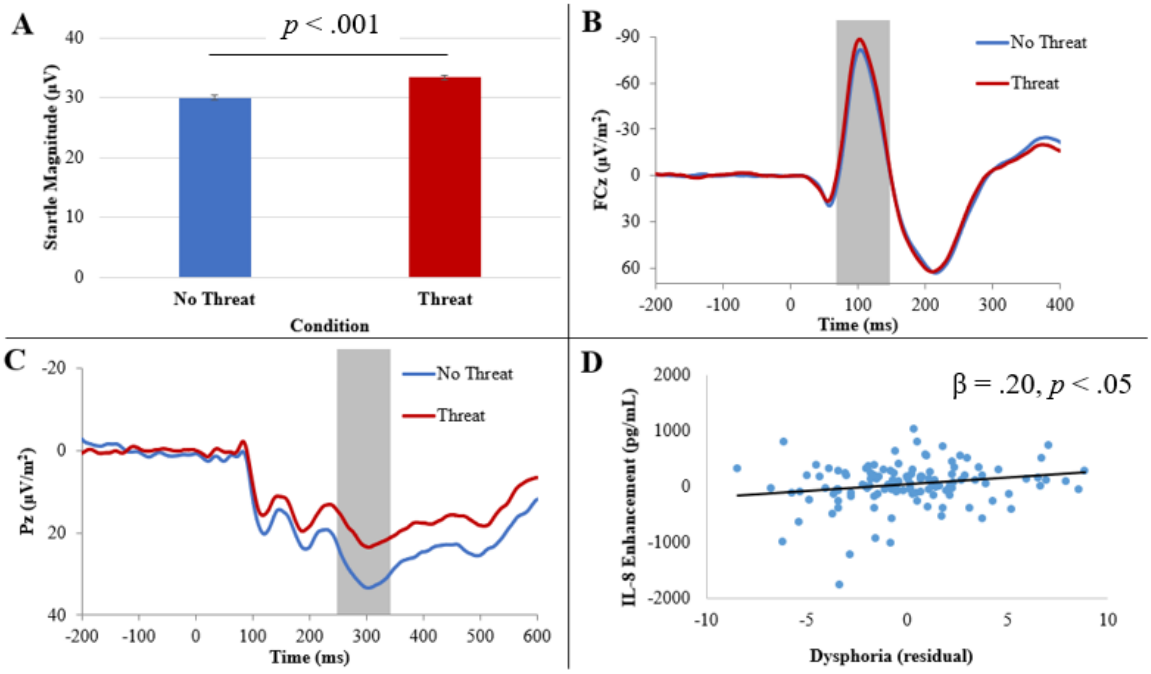
**Support:** SUNY at Stony Brook 830036

**Title:** Threat-enhanced immune response and depression

**Authors: *R. A. FERRY**, B. D. NELSON;
Psychology, Stony Brook Univ., Stony Brook, NY

**Abstract:** Threat enhances neurobiological indicators of defensive motivation and attention. Social threat has been shown to also elicit an enhanced immune system response, but it is unclear whether non-social threat (e.g., shock) also elicits an enhanced immune system response. Immune activation has also been linked to depression, such that a larger immune response is associated with greater depressive symptoms. No study has examined whether this relationship exists in the context of non-social threat. In a sample of 123 young adults, the present study used a between-subjects design to examine the startle reflex and both probe N100 and P300 event-related potentials during a modified no, predictable, and unpredictable threat (NPU-threat) task

using electric shocks. Saliva samples were collected via passive drool before and after the NPU-threat task to assess IL-6, TNF-α, IL-1β, and IL-8. Current depression and anxiety symptoms were assessed using the Inventory of Depression and Anxiety Symptoms - Expanded Version. The startle reflex, probe N100, and probe P300 were all modulated by threat, relative to no threat, such that the startle reflex was potentiated, the probe N100 was enhanced, and the probe P300 was suppressed. Across all participants, IL-6 and TNF-α decreased after threat exposure, irrespective of whether the threat was predictable or unpredictable. However, a greater increase in IL-8 after threat exposure was associated with greater depression symptoms. The present study suggests that a non-social threat can elicit increased neurobiological defensive motivation and attention. Further, a non-social threat elicits an increased immune response but only among people who endorsed greater depressive symptoms.




a) Startle magnitude across different levels of threat condition. ERP waveforms for the probe N100 (b) and the probe P300 (c) across the threat conditions. Shaded regions indicate the segments where mean activity was scored. d) Scatterplot of interleukin-8 enhancement in response to threat and self-reported depression symptoms.

**Disclosures:** **R.A. Ferry:** None. **B.D. Nelson:** None.

**Poster**

**PSTR035. Stress and Neuroimmunology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR035.07/FF6

**Topic:** F.03. Stress and the Brain

**Title:** From stress to inflammation. Psychoneuroimmunoendocrinological response to adverse childhood experiences in students.

**Authors: *D. GUÍZAR**[1], A. ÁLVAREZ-VIDES[2], P. RODRÍGUEZ PARTIDA[2];
[1]Univ. Nacional Autónoma De México, México, Mexico; [2]Natl. Inst. of Psychiatry Mexico, MEXICO CITY, Mexico

**Abstract:** Introduction: Brain development is a multifaceted process regulated by genes and shaped by environmental experiences. Early stress and exposure to traumatic events negatively affect the nature and trajectory of normal development.Methods: A literature review of the main psychiatric diagnoses associated with childhood adversity and the neurophysiological mechanism involved was conducted followed by a cross-sectional study with 2457 students in Mexico. The Adversity in Childhood International Questionnaire (ACE-IQ) was used to assess ACEs, including forms of psychological, physical and sexual abuse, as well as dysfunction in the home; the Depression Scale (PHQ-9), Beck anxiety inventory, Alcohol Use Disorders Identifications Test (AUDIT) and Drug Abuse Screening Test (DAST-10) for substance use. Multiple logistic regression models were used to examine associations between ACE global score, PHQ-9, and medical and mental health risk behaviors/comorbidities after controlling for potential confounders.Results: 73.8% of participants reported at least one ACE, and 13.2% reported four or more ACEs. Increased ACEs were associated with increased risk of alcohol use (adjusted odds ratio [AOR] = 2.17, 95% confidence intervals [CI] 2.09-2.56), psychoactive substance use (AOR = 4.17, 95% CI 2.71-5.18), depression (AOR = 3.73, 95% CI 3.51-3.84), and suicide risk (AOR = 1.23, 95% CI 1.03-1.42) in adulthood. When confounders were taken into account, the effects of each RCT component on risk behavior and health varied.Discussion: When individuals experience adversity, they often mobilize endocrine, immune, and nervous system responses that, in turn, involve neuroplasticity mechanisms that prepare them to respond to learned environmental contingencies and future threats. In this study, ACEs were associated with increased odds of risky behaviors and mental disorders in adulthood after controlling for relevant demographic and socioeconomic factors.

**Disclosures: D. Guízar:** None. **A. Álvarez-Vides:** None. **P. Rodríguez Partida:** None.

**Poster**

**PSTR035. Stress and Neuroimmunology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR035.08/FF7

**Topic:** F.03. Stress and the Brain

**Support:** R01 Grant DK124792

**Title:** The role of heme and hemopexin in urologic chronic pelvic pain syndrome in mice

**Authors: *A. GRYSHYNA**[1], C. DEWITTE[2], F. VENDRAME[2], R. PATEL[2], J. DEBERRY[3]; [1]Univ. of Alabama at Birmingham Chapter, Birmingham, AL; [2]Univ. of Alabama at Birmingham, Birmingham, AL; [3]Univ. of Alabama At Birmingham Sch. of Medi, Birmingham, AL

**Abstract: Introduction:** Urologic chronic pelvic pain syndrome (UCPPS) is a chronic pain condition characterized by pelvic hypersensitivity, often presenting with increased urinary frequency and urgency. Currently, the etiology of UCPPS is unclear and likely multifaceted which makes it difficult to develop effective therapeutics. Epidemiological data suggest stress is an important factor in pain associated with UCPPS in a sex-dependent fashion. Metabolism of heme, an organic porphyrin molecule, has been linked with both stress and regulation of nociceptive processes. However, a role for heme in pain associated with UCPPS has not been explored. Hemopexin (HPX) is a heme scavenging protein that transports free heme to the liver for degradation. The aim of the current study was to explore the relationship between stress, heme scavenging, and pelvic/visceral nociception in HPX-deficient mice.**Methods:** Adult male and female HPX knockout (KO) mice and wild type (WT) littermate controls were included in all experiments. Sensory testing was performed to assess hindpaw, pelvic floor, and urinary bladder sensitivity at baseline and following exposure to acute water avoidance stress (WAS). A simplified up-down method with von Frey monofilaments was used to assess mechanical sensitivity of the pelvic region and hindpaw. The void spot assay VSA) was used to quantify spontaneous urine voiding. In female mice, visceromotor responses (VMRs) to bladder distension were subsequently quantified to assess bladder nociception. All of the experiments were approved by the Institutional Animal Care and Use Committee (IACUC) at University of Alabama at Birmingham. **Results:** The results demonstrate that, overall, HPX KO mice had significantly greater mechanical sensitivity in the pelvic region ($p<.001$) but not in the hindpaw. A significant sex difference in number of voids and total area of voids during VSA was observed ($p<.001$). Following WAS exposure, female HPX KO mice had significantly greater VMRs compared to WT ($p<0.05$, one-tailed). **Conclusions:** These findings indicate that although hemolysis may be a systemic phenomenon, some tissues or organs, like bladder, are more susceptible to hemolytic effects.

**Disclosures: A. Gryshyna:** None. **C. DeWitte:** None. **F. Vendrame:** None. **R. Patel:** None. **J. Deberry:** None.

**Poster**

**PSTR035. Stress and Neuroimmunology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR035.09/FF8

**Topic:** F.03. Stress and the Brain

**Support:** NJHF PC-164-23

**Title:** Chronic stress induces sex-dependent neuroinflammation physiological dysregulation in the rodent locus coeruleus

**Authors:** A. REYES[1], ***D. CHANDLER**[2];
[1]Cell Biol. and Neurosci., Rowan-Virtua Sch. of Osteo. Med., Stratford, NJ; [2]Rowan-Virtua Univ. Sch. of Osteo. Med., Stratford, NJ

**Abstract:** Stress is a physiologic neuroendocrine response to a stressor that promotes organism survival through adaptive biological processes and behaviors. While adaptive in the short term, chronic or traumatic stress are known risk factors for the development of anxiety disorders. Other key risk factors in the development of anxiety disorders have also been identified, such as sex. Generally, females have higher rates of anxiety disorder diagnosis than males. In response to stress, stress-responsive systems such as the Hypothalamus-Pituitary-Adrenal (HPA) axis and the locus coeruleus (LC)-Norepinephrine (NE) system are activated. Chronic activation however can disrupt negative feedback loops that suppress their function and contribute to HPA axis and LC-NE system dysregulation, often leading to anxiety-like phenotypes in animal models. Studies have also demonstrated the role of chronic stress in inducing neuroinflammation. However, The role of sex and the link between chronic stress exposure, neuroinflammation, and LC dysregulation in the development of anxiety-like behaviors has not been elucidated. This study demonstrates the sex-dependent neuroinflammatory and neuronal changes in the rodent LC using elevated plus maze (EPM), ex-vivo electrophysiology, and immunohistochemistry (IHC). To model chronic stress, male and female adolescent (8-week-old) Sprague Dawley rats were restrained and exposed to predator odorant for two hours per day for ten days over two consecutive weeks. Here we report that stressor exposure leads to increased anxiety-like behavior in the elevated plus maze, an effect that was accompanied by increased LC spontaneous firing frequency as well as disruption of other measures of LC neuronal physiology. IHC staining for IBA-1, a microglial marker, and Major histocompatibility II (MHC-II), an activation marker within the LC, reveals a reveal a significant increase in penetrance of LC by activated microglia in stressed males relative to controls. In contrast, an opposite trend was noted in females. Furthermore, correlation analysis between percent weight change, a measure of stress induction, and IBA-1 cell counts within the LC demonstrates a significant negative correlation in males but no correlations in females, suggesting increased male LC neuroinflammation in response to chronic stress. Our results indicate that chronic stress exposure induces sex-dependent LC neuroinflammation, which may lead to alterations in LC neuronal physiology and influence rodent anxiety-like behaviors.

**Disclosures:** **A. Reyes:** None. **D. Chandler:** None.

**Poster**

**PSTR035. Stress and Neuroimmunology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR035.13/FF9

**Topic:** F.03. Stress and the Brain

**Support:** NIMH R01MH127820
NIMH R01MH104559
BBRF NARSAD Young Investigator Grant 31140

**Title:** Neuroimmune mechanisms underlying chronic stress-induced reward deficits

**Authors: *R. L. FISHER-FOYE**[1], R. DURAND-DE CUTTOLI[1], F. CATHOMAS[1], L. F. PARISE[1], A. V. AUBRY[1], L. LI[1], S. COSTI[2], E. J. NESTLER[1], J. W. MURROUGH[2], S. J. RUSSO[1];
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**Abstract:** Major depressive disorder (MDD) is a leading cause of disability worldwide, creating an immense burden on countless individuals and the greater global population. One prominent symptom associated with MDD, is anhedonia: the loss of interest for hedonic stimuli. In parallel, several clinical and pre-clinical studies have linked exposure to stress and MDD, a stress-related psychiatric disorder, with alterations of the peripheral immune system. However, the neuroimmune mechanisms that lead to brain circuit alterations and ultimately to behavioral alterations are not well understood. Here, we investigate the impact of stress on blood-brain barrier (BBB) integrity, peripheral immune marker infiltration into the brain, and subsequent effects in brain reward centers controlling anhedonia. We then assess reward deficits in a mouse version of the probabilistic reward task (PRT) after chronic exposure to social defeat stress (CSDS) and with or without manipulating BBB integrity or peripheral immunity. This task, first developed in humans, is well-positioned to extract stress-induced reward deficits relevant to MDD. Our group has shown that, in mice exposed to CSDS, alterations of the BBB lead to infiltration of peripheral monocytes into the ventral striatum. Here, we found that a direct consequence of this infiltration is a perturbation of the neuronal function in the nucleus accumbens and subsequent reward sensitivity deficits in the PRT. Namely, following CSDS, susceptible mice showed a blunted response bias but not unstressed control or resilient mice. Next, we found that artificially opening the BBB using a viral knock-down of the Claudin-5 tight junction protein led to an exaggerated impact of a sub-threshold stressor on reward sensitivity in the PRT. Our results indicate that chronic stress causes systemic inflammation and that alterations of the BBB lead to an infiltration of immunity markers into the ventral striatum, altering neuronal function and, ultimately, causing major reward deficits. To bring a translational dimension to this project, we work with the Depression and Anxiety Center at Mount Sinai on using human PRT datasets and blood samples to inform our preclinical findings through an existing liquid biomarker pipeline established by our groups. This study provides a better understanding of the neuroimmune influence on reward deficits in MDD and offers new perspectives in the development of new personalized immune-based therapeutics to treat depression.

**Disclosures: R.L. Fisher-Foye:** None. **R. Durand-De Cuttoli:** None. **F. Cathomas:** None. **L.F. Parise:** None. **A.V. Aubry:** None. **L. Li:** None. **S. Costi:** None. **E.J. Nestler:** None. **J.W. Murrough:** None. **S.J. Russo:** None.

**Poster**

**PSTR035. Stress and Neuroimmunology**

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**Topic:** F.03. Stress and the Brain

**Support:** CIHR 201811MFE-414896-231226
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NIH R01MH127820

**Title:** Stress-activated brain-gut circuits regulate intestinal inflammation and barrier permeability

**Authors: *K. CHAN**, L. LI, L. PARISE, F. CATHOMAS, K. B. LECLAIR, Y. SHIMO, H.-Y. LIN, R. DURAND-DE CUTTOLI, A. AUBRY, A. OSMAN, C. YUAN, J. ALVAREZ, T. DRESCHER, M. P. KASTER, J. WANG, S. RUSSO;
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**Abstract: BACKGROUND:** Stress disorders such as 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.

**Disclosures: K. Chan:** None. **L. Li:** None. **L. Parise:** None. **F. Cathomas:** None. **K.B. LeClair:** None. **Y. Shimo:** None. **H. Lin:** None. **R. Durand-De Cuttoli:** None. **A. Aubry:**

None. **A. Osman:** None. **C. Yuan:** None. **J. Alvarez:** None. **T. Drescher:** None. **M.P. Kaster:** None. **J. Wang:** None. **S. Russo:** None.

**Poster**

**PSTR035. Stress and Neuroimmunology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

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**Topic:** F.03. Stress and the Brain

**Support:** BBRF NARSAD Young Investigator 31194
NIMH R01MH127820
NIMH R01MH104559

**Title:** Alterations to the blood-brain barrier promote changes in alcohol preference.

**Authors: *L. PARISE**, K. CHAN, F. CATHOMAS, L. LI, R. DURAND DE-CUTTOLI, H.-Y. LIN, A. AUBRY, C. YUAN, J. ALVAREZ, R. L. FISCHER-FOYE, T. DRESCHER, S. J. RUSSO;
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**Abstract:** Background: Major depression is a serious public health concern and is commonly comorbid with alcohol use and abuse. Previous work highlights the role of blood brain barrier (BBB) tight junctions in appropriate stress-responding, but less is known about how these proteins are involved in alcohol-related behaviors. To address this gap, the following experiments investigated the role of Claudin 5 (CLDN5), the tight junction protein, in stress-induced alterations in alcohol reward. Methods: Adult male mice were exposed to chronic social defeat stress and then given intermittent access to alcohol (20%; three 24-hour bouts/week) in a volitional drinking paradigm that models moderate binge drinking and is thus very relevant to both recreational and potentially problematic alcohol consumption. After eight weeks of alcohol exposure mice were tested in a behavioral battery to assess stress reactivity. To further investigate the role of CLDN5in alcohol reward we adopted a virally-mediated approach to down-regulate CLDN5 in the nucleus accumbens and assessed alcohol-related behaviors (escalating preference paradigm [water vs alcohol 3, 6, 10, 20%] and alcohol conditioned-place preference (CPP) [1.0 and 2.0 mg/kg]). Results: Stress-exposed mice drank more alcohol across the duration of the drinking paradigm and did not show any attenuation of stress-related deficits. Knockdown of CLDN5 in nucleus accumbens (NAc) of male mice increased their drinking behavior at lower doses of alcohol (3%) compared to their control counterparts. In a separate group of mice we assessed the effects of CLDN5 knockdown in NAc on alcohol CPP and found that Claudin 5 knockdown promoted preference for lower doses of alcohol. Interestingly, exposure to a subthreshold stressor shifted alcohol preference regardless of CLDN5 knockdown. Conclusions: These data suggest that alcohol-induced stress-susceptibility can be recapitulated by artificially opening the BBB. Furthermore, in the absence of stress or alcohol, artificial downregulation of CLDN5 shifted the rewarding properties of alcohol by enhancing preference

for lower concentrations of alcohol. These data highlight that BBB integrity plays a role in the rewarding properties, and thereby abuse liability, of alcohol.

**Disclosures:** **L. Parise:** None. **K. Chan:** None. **F. Cathomas:** None. **L. Li:** None. **R. Durand de-Cuttoli:** None. **H. Lin:** None. **A. Aubry:** None. **C. yuan:** None. **J. Alvarez:** None. **R.L. Fischer-Foye:** None. **T. Drescher:** None. **S.J. Russo:** None.

**Poster**

**PSTR035. Stress and Neuroimmunology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR035.16/FF12

**Topic:** F.03. Stress and the Brain

**Title:** Hepatic sympathetic innervation regulates acute-phase protein production

**Authors: *E. AVISHAI**, H. HAYKIN, N. T. BOSHNAK, M. SIROTKIN, Z. ZBEIDAT, T. HARAN, R. YIFA, M. SAMMONS, M. KROT, T. KOREN, I. ZALAYAT, M. AMER, D. FARFARA, H. AZULAY-DEBBY, A. ROLLS;
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**Abstract:** Acute-phase proteins (APP) are liver-produced plasma proteins, whose concentration changes in the blood during inflammation. APPs include proteins of the complement pathway, coagulation cascade, transporter proteins, antiproteases, hormone regulating proteins and many more. They are involved in restoring homeostasis, regulating the immune response, protein transport, and tissue protection from damage, therefore, are considered as part of the innate immune response. The APP response has been an indicator of inflammation, but recent studies hint that non-inflammatory, psychological stress can induce APP response. However, the mechanism that induces the APP response during stress remains unknown. In our study, we map APP changes after stress and reveal the mechanism behind this phenomenon. We track selected APP expression in the liver following two different stress models in mice - restraint stress and swim stress. We show that psychological stress without inflammation can induce robust changes in APP expression in the liver for example, mannose-binding lectin 2 showed 30% reduction after restraint stress (control 1±0.03, restraint stress 0.7±0.02, t.test, p.value<0.0001) and 20% increase after swim stress (control 1.02±0.07, swim stress 1.2±0.06, t.test, p.value<0.05). During stress, the brain activates two main pathways - the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). We demonstrate that the HPA axis is not involved in this process - artificial activation of this axis by corticosterone and inhibition of this axis by adrenalectomy does not affect APP transcription in the liver. However, injection of noradrenaline (NA), the mediator of the SNS, recapitulates most of the change in APP shown after stress while blockade of this axis abolishes APP changes after stress. SNS activation can result in pro-inflammatory cytokines such as interleukin 6 (IL-6) which is the key regulator of APP in an inflammatory context. However, IL-6 receptor blockade did not affect APP changes seen after NA injection implying the involvement of a different mechanism in stress-induced changes in

APP. Therefore, to assess the direct effect of NA on the liver we stimulated hepatocytes ex-vivo with NA which resulted in changes in APP expression demonstrating the capacity of local activation of the hepatic SNS to modulate APP expression. This is a novel mechanism of neuronal control over one of the fundamental processes that were attributed solely to inflammatory signals. The local SNS in the liver can alter the hepatocytes' protein production and activate APP response, therefore, regulate systemic physiology.

**Disclosures:** **E. Avishai:** None. **H. Haykin:** None. **N.T. Boshnak:** None. **M. Sirotkin:** None. **Z. Zbeidat:** None. **T. Haran:** None. **R. Yifa:** None. **M. Sammons:** None. **M. Krot:** None. **T. Koren:** None. **I. Zalayat:** None. **M. Amer:** None. **D. Farfara:** None. **H. Azulay-Debby:** None. **A. Rolls:** None.

**Poster**

**PSTR035. Stress and Neuroimmunology**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR035.17/FF13

**Topic:** F.03. Stress and the Brain

**Support:** NIH Grant R56MH124930-01A1
NARSAD Young Investigator Grant 24805

**Title:** Chronic Variable Stress Leads to Sex-Specific Gut Alterations

**Authors: *D. KROPP**, J. RAINVILLE, M. GLOVER, S. CLINTON, G. HODES;
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**Abstract:** Alterations of the gut microbiome contribute to various inflammatory disorders including major depression, autism spectrum disorder, and anxiety disorders. These disorders have been linked to changes in systemic inflammation and circulating levels of cytokines. The 'leaky gut' hypothesis (Maes et al, 2008) suggests that peripheral inflammation may result from leakiness of the gut intestinal barrier, thereby permitting gut microbiota, metabolites, and/or cytokines to infiltrate other parts of the body, including the brain. Chronic stress is a well-known trigger for emotional disorders, and stress has been shown to shift gut microbiota composition, however this body of research was largely conducted in only male mice. Depression and anxiety disorders are 2x more likely to occur in women than men, mechanisms underlying this effect remain poorly understood. Here we examined how chronic stress alters gut compositions over time in male and female C57BL/6J mice. We exposed male and female mice to a variable stress paradigm that consists of three stressors (2 second foot shocks across 1hour; restraint for 1 hour; tail suspension for 1 hour) alternated daily during a set stress period. In the present study, we hypothesized that variable stress would trigger changes in the gut microbiome of male and female subjects' sex specifically, and that these changes would be correlated strongly with circulating cytokines at the timepoint where dysbiosis is observed. Thus, male and female mice were exposed to 28-days of variable stress or control condition (n=6 per group). Fecal samples

were collected from all subjects at three time points: before stress; after 6-days, and after 28-days of variable stress (or control condition). Fecal samples were prepared for next-generation sequencing; 16S rRNA amplicon sequencing data was collected and analyzed utilizing RStudio and various 16s amplicon sequencing and statistical analytics packages (DADA2, Phyloseq, DESeq2, and Corrplot). We found that there were more microbial changes in males compared to females following 28-days of variable stress. Relative abundance of the microbial families Erysipelotrichaceae and Lactobacillaceae were altered in opposite directions sex dependently. Cytokines involved in eosinophil-related immune activity were altered in males and females following stress and are correlated with significantly altered microbes. This exploratory analysis of compositional changes in the gut will elucidate some of the mechanisms by which stress dysregulates mood via the microbiome-gut-brain-axis in a sex specific manner.

**Disclosures:** **D. Kropp:** None. **J. Rainville:** None. **M. Glover:** None. **S. Clinton:** None. **G. Hodes:** None.

**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.01/FF14

**Topic:** F.03. Stress and the Brain

**Support:** KSN2211010

**Title:** Electric foot shock-induced chronic stress enhances anxiety-like behavior and alters the gut microbiome in mice

**Authors: *J. KIM**, M.-S. KIM, H. KIM, K.-I. LEE, H. KIM, K.-S. PARK;
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**Abstract:** Chronic stress causes physical and mental disorders and leads to weakened immune system. This is associated with a bidirectional pathway that includes complex interactions between the gut and brain. The host's microbiome can play a role in regulating this gut-brain axis. Therefore, it is important to elucidate the relationship between chronic stress and the gut microbiota, but it is poorly understood. In this study, we investigated behavioral changes and alteration in gut microbiome composition in mice exposed to chronic stress induced by electric foot shock. We conducted behavioral evaluation through an open field test. We extracted mice brain at the end of the experiment and measured their weight. Body weight can be an indicator of pain experienced by the animal. Therefore, it was monitored until the end of the experiment. We collected feces from chronic stress-induced mice for microbiome analysis through 16S rRNA-based taxonomic profiles. We found that electric foot shock-induced chronic stress resulted in increased anxiety-like behavior and decreased brain weight. In the foot shock group, body weight and weight gain decreased compared with the control group, but it did not decrease compared to before the experiment. The foot shock group had altered gut microbiota

characterized by increased Firmicutes/Bacteroidetes ratio and decreased species richness. At the species level, the foot shock group had higher abundance of *Faecalibaculum rodentium*, *Clostridium celatum group*, *Lactobacillus murinus group*, *Lactobacillus reuteri group*, and *Lactobacillus gasseri group* and lower abundance of *Helicobacter japonicus*, *Akkermansia muciniphila* and *Lactobacillus intestinalis* than the control group. Our results suggest that the gut microbiome may play a role as a key regulator of physiological pathogenesis caused by chronic stress.

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**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.02/FF15

**Topic:** F.03. Stress and the Brain

**Support:** NIH RO1 DK126740
NIH F31 HL168820

**Title:** Stress modulation by an ascending catecholaminergic-melanocortin pathway

**Authors: *C. LAULE**[1], *C. LAULE[2], N. SAYAR-ATASOY[1], H. KIM[1], T. ATES[1], D. ATASOY[1];
[1]Neurosci. and Pharmacol., [2]Univ. of Iowa, Iowa City, IA

**Abstract:** Physiological and psychological forms of stress influence appetite and impose significant health burdens. However, the neural substrates underlying stress and feeding responses are unresolved. Adrenergic tyrosine hydroxylase (TH) neurons in the nucleus tractus solitarius (NTS) respond to stress, yet their downstream targets are not well-established. We have shown that $NTS^{TH}$ inhibits melanocortin-4 receptor (MC4R) neurons in the paraventricular hypothalamus (PVH) and activation of this pathway is important for hypoglycemic hunger, a form of physiological stress. Based on the capacity of $NTS^{TH}$ neurons to respond a variety of stressors, we hypothesized that $NTS^{TH}\rightarrow PVH^{MC4R}$ function as a general stress effector circuit. As an initial step towards testing this hypothesis, we performed fiber photometry to monitor how various stressors influence circuit dynamics. With Axo-GCaMP, we found that physiological and psychological stressors robustly activate $NTS^{TH}$ axons in the PVH. Using the fluorescent norepinephrine reporter, NE2h, we found that stress-induced $NTS^{TH}$ projection activity is mirrored by rapid norepinephrine release onto $PVH^{MC4R}$ neurons. Using GCaMP, our results show that stress also inhibits $PVH^{MC4R}$ neurons. These responses are consistent with a stress sensitive inhibitory $NTS^{TH}\rightarrow PVH^{MC4R}$ connection. We next assessed the functional role of $PVH^{MC4R}$ neurons on emotional valence. A conditioning/real-time place preference assay with halorhodopsin showed that $PVH^{MC4R}$ suppression is aversive. Lastly, we found that

chemogenetic $PVH^{MC4R}$ activation blocks LiCl-induced aversion, suggesting that $PVH^{MC4R}$ inhibition is necessary for negative valence caused by LiCl. Taken together, our findings indicate a critical role for the $NTS^{TH}$→$PVH^{MC4R}$ pathway in stress response. Based on the importance of $NTS^{TH}$ and $PVH^{MC4R}$ neurons in appetite, future experiments are needed to clarify the role of this circuit in stress related feeding disorders.

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**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.03/FF16

**Topic:** F.03. Stress and the Brain

**Title:** Stress responsive grooming of Fischer 344 rats in elevated plus maze and home cage conditions.

**Authors: *A. C. GLORIUS**, J. P. HERMAN;
Univ. of Cincinnati, Reading, OH

**Abstract:** Obsessive Compulsive Disorder (OCD) is a highly disruptive chronic condition that affects approximately 1.2% of the adult U.S. population. OCD is commonly characterized by the presence of thoughts (obsessions) that trigger the execution of repetitive behaviors (compulsions). Rodent models of OCD typically examine highly stereotyped behaviors such as grooming. Self-grooming increases in the presence of stress in numerous rodent models. Mechanisms underlying this process remain to be delineated. We propose that a stressor triggers activation of BLA, synapses in the NAc, which in turn drives a striatonigral pathway known to induce grooming. We used tracing approaches in Fischer 344 rats to assess this pathway. Rats received a unilateral PHA-L (anterograde tracer) iontophoretic injection in the BLA and a complimentary ipsilateral/unilateral red Retrobead (retrograde tracer) injection in the SNr. We identified PHA-L labeled terminals in both the NAc and in the ventromedial aspect of the SNr, indicating the existence of BLA projections. Subsequent experiments examined grooming (in multiple contexts) as a parameter for stress-responsive behavior, as a means of identifying a reproducible model of stress grooming. Fischer 344 rats (a strain known for high levels of grooming) were exposed to two versions of elevated plus maze (EPM) tests (traditional/closed arm removal) paired with restraint stress. F344 rats exhibiting low baseline grooming significantly increased grooming behavior in the traditional EPM test following restraint exposure, consistent with stress enhancement of behavior. Removal of the EPM close arm enclosure in EPM-trained markedly increased grooming behavior in all rats, consistent with selection of an alternative coping strategy in the absence of the darkened recess. These data identify behavioral strategies to 1) explore individual differences in stress-induced grooming and 2) test the ability to increase grooming behavior by removal of environmental safety signals.

Follow-up studies tested the role of BLA◊NAc circuitry in control of stress-induced grooming. F344 rats infused with Gq DREADD in BLA◊NAc projections were exposed to CNO injected in home cage conditions (to test the strength of the pathway in the absence of stress cues) and in the context of EPM+restraint with closed arm removal. These studies test whether BLA circuitry subserve a stress-coping in an anxiety context.

**Disclosures: A.C. Glorius:** None. **J.P. Herman:** None.

**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.04/FF17

**Topic:** F.03. Stress and the Brain

**Title:** Directional Shifts Shape Neural Trajectories of Emotion Transitions

**Authors: *Y. HAO**[1], K. BO[2];
[1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Dartmouth Col., Hanover, NH

**Abstract:** Humans frequently transition between different emotional states, each eliciting a unique neural pattern. These transitions can be conceptualized as neural trajectories, representing the underlying dynamic changes in emotional neural patterns. However, it is unknown whether these neural trajectories remain consistent or vary depending on the direction of the shift (e.g., neutral to negative vs. negative to neutral). The neural trajectory of the present emotional state can be influenced by past experiences, such as prior stimuli, as well as stressful life events. This highlights the inherent nature of the human brain and its potential impact on emotional processing based on history. To better understand this, we conducted an EEG experiment with 40 healthy college students (50% females).Participants viewed sequences of four images (two neutral, two negative, each 4.5 seconds) from the IAPS collection. Affect transition was induced by changing from neutral to negative or negative to neutral conditions, repeated 18 times. We applied support vector machine to decode the opposite neural trajectories pair ( neutral to negative and negative to neutral). Our results revealed the following: 1) Neural trajectories 'neutral to negative' and 'negative to neutral' were robustly decoded above chance (Group average accuracy = 56.1%, $p = 0.00017$). 2) This differentiation was associated with increased frontal alpha power and decreased frontal beta power. 3) Individuals with lower perceived stress showed marginally greater differentiation in neural trajectories compared to those with higher stress levels (two-sample t-test, $t = 1.96$, $p = 0.06$).These findings suggest that the direction of emotional shift critically influences neural trajectories between emotional states. Moreover, these trajectories may contribute to adaptive responses and behaviors, as indicated by the relationship with perceived stress.In summary, our study elucidates the dynamics of emotional transitions and highlights the role of neural trajectories in adaptive processes. These findings contribute to our understanding of emotional regulation mechanisms and may inform interventions targeting emotional well-being.

**Disclosures:** **Y. Hao:** None. **K. Bo:** None.

**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

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**Topic:** F.03. Stress and the Brain

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Merit Award 1I01BX003512 from the U.S. Department of Veterans Affairs Biomedical Laboratory Research and Development Program
a grant from the William and Ella Owens Medical Research Foundation

**Title:** The role of the projection from medial prefrontal cortex to lateral septum in coping behaviors

**Authors: *J. LIU**[1], K. TABISOLA[1], A. R. KNIPPENBERG[1], L. F. FERREIRA[1], D. A. MORILAK[2];
[1]UT Hlth. Sci. Ctr. at San Antonio, San Antonio, TX; [2]Univ. of Texas Hlth. Sci. Ctr. at San Antonio, UT Hlth. Sci. Ctr. San Antonio Dept. of Neurosci., San Antonio, TX

**Abstract:** Coping involves behavioral and cognitive processes that enable one to respond and adapt to stress. Coping strategies can be active or passive. Active coping is associated with less stress, and depressive symptoms, whereas passive coping (i.e., avoidance) is often maladaptive. Effective coping strategies play an important role in preventing stress-induced neuropsychiatric conditions, but little is known about the underlying biological processes and neurocircuitry that regulate effective coping strategies. The shock-probe defensive burying (SPDB) test is a well-established animal model to test the coping behaviors of rodents. Our previous studies showed that adrenergic receptor signaling and galanin signaling in the lateral septum (LS) differentially regulated defensive burying responses (active coping) and immobility (passive coping) in the SPDB test. The LS receives glutamatergic input from the medial prefrontal cortex (mPFC), which has been implicated in the modulation of stress-related behaviors including the impairment of coping behaviors. Therefore, in the current study, we proposed that the mPFC-LS pathway is involved in the regulation of coping behaviors in the SPDB test. To test this hypothesis, a retrograde AAV5 virus that expresses Cre recombinase (rgAAV-Cre) and a virus to deliver a recombinase-dependent designer receptor exclusively activated by designer drugs (DREADD) were injected into LS and mPFC, respectively. In non-stressed rats, chemogenetic inhibition of the mPFC-LS pathway decreased active burying and shifted coping behavior from active to passive, indicated by a decrease in the burying ratio (bury time/bury time + immobility time). When the mPFC-LS pathway was activated by a Gq-DREADD, there was no effect on immobility or burying. Chronic unpredictable stress (CUS) induced a significant decrease of the burying ratio compared with non-stressed rats. Chemogenetic activation of mPFC -LS pathway reversed the effect of CUS by decreasing the latency to bury, reducing immobility, and restoring

the burying time and bury ratio to unstressed control levels. Our results suggested that mPFC-LS pathway plays an important role in modulating coping responses to environmental stimuli.

**Disclosures: J. Liu:** None. **K. Tabisola:** None. **A.R. Knippenberg:** None. **L.F. Ferreira:** None. **D.A. Morilak:** None.

**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.06/FF19

**Topic:** F.03. Stress and the Brain

**Support:** NIH Grant HD099338

**Title:** Post-traumatic stress disorder and the hyperarousal of reflexes in the rat model

**Authors: *M. D. SMITH**, B. G. SCHREURS, L. BAYS, E. IREWOLE;
Neurosci., West Virginia Univ., Morgantown, WV

**Abstract:** Previous research has shown that adverse experiences can cause profound, lifelong changes in the brain and behavior, with the bulk of knowledge surrounding combat-related post-traumatic stress disorder (PTSD). Many symptoms seen in individuals suffering from PTSD—anxiety, aggression, etc.—can be categorized as hyperarousal symptoms. a. Changes in reflexes to these pulses (unconditioned responding, UR) following dEBC are denoted as conditioning-specific reflex modification (CRM), and this is used to represent the hyperarousal of reflexes seen in PTSD. To explore a potential mechanism for this, we are examining the role of the perineuronal net (PNN). PNN maturation in early life coincides with the closure of the critical period of learning in several brain regions, prior to which an individual's experiences do not result in recorded memory. Altered development of the PNN during this critical period may be responsible for hyperarousal of the eyeblink UR, especially in the deep cerebellar nuclei (DCN) and basolateral amygdala (BLA), two structures shown to be heavily involved in sensorimotor learning. We use confocal microscopy on brain slices to visualize *Wisteria floribunda agglutinin* (WFA)-stained PNN and MAP2-stained neuronal soma. In the BLA and DCN tissue of rats undergoing paired conditioning, we expect to see a higher ratio of WFA+/MAP2+ signal compared to controls, representing a greater density of PNN-positive neurons. Preliminary behavioral data suggests that paired dEBC rats do show hyperarousal in the form of CRM. Analysis of posttest EMG responses to the series of periorbital pulses show a peak latency that is left-shifted, a higher peak amplitude, and a "double-peak" UR morphology in paired animals when compared to pretest, which was not seen in the unpaired group. Prior published data from our lab shows a higher density of PNN-positive neurons in paired dEBC animals, and that animals with a digested PNN have conditioned eyeblink responses (CRs) with smaller amplitudes and with smaller areas compared to saline-administered vehicle rats. This study aims

to establish CRM in the rat in order to further support CRM as a model for PTSD-like hyperarousal, by showing this behavioral modification in a second species of animal model.

**Disclosures: M.D. Smith:** None. **B.G. Schreurs:** None. **L. Bays:** None. **E. Irewole:** None.

**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.07/FF20

**Topic:** F.03. Stress and the Brain

**Support:** ERC Advanced Grant
MILAB

**Title:** Excitatory and inhibitory afferents of the paraventricular thalamic nucleus.

**Authors: *L. BIRO**[1], Z. BUDAY[1], K. KÓTA[1], Á. BABICZKY[2], F. MÁTYÁS[1], L. ACSADY[1]; [2]Neuronal Network and Behavior Res. Group, [1]Inst. of Exptl. Med., Budapest, Hungary

**Abstract:** The paraventricular thalamic nucleus (PVT) innervates several forebrain areas through their excitatory axon collaterals and are involved in important emotional and motivational functions. Activation or inhibition of PVT result in major changes in processing fear, arousal or stress related signals and alteration in homeostatic behaviors indicating that the optimal balance of excitation and inhibition is essential for its function. However, the origins of glutamatergic and GABAergic afferents to PVT is presently unclear. A major cell population of PVT contains calretinin (CR). These cells provide most of the thalamic inputs to the prelimbic cortex, amygdala and n. accumbens and selectively express c-Fos following stress. Whether PVT/CR+ neurons also selective regarding their afferentation remains to be established. Thus, in this study we aimed to explore i; the origins of excitatory and inhibitory inputs to PVT. ii; how selective these inputs are for PVT/CR+ cells iii; to what extent the different inputs converge or segregate in the PVT. In our experiments, we used retrograde and anterograde viral labelling in vGLUT2-Cre, vGAT-Cre, and vGLUT2-Cre/vGAT-Flp double transgenic mouse strains to analyse subcortical inputs and Rbp4-Cre, NTSR1-Cre, FoxP2-Cre strains to label cortical inputs. We found that the subcortical afferents to PVT are widely distributed but the origin of excitatory and inhibitory inputs largely segregate. Co-innervation of PVT by both GABAergic and glutamatergic afferents was only observed from the periaqueductal gray. Axons from different subcortical areas overlapped significantly and were highly selective for the CR+ zone in the core region of PVT. In contrast the majority of cortical inputs arising from layer 5 pyramidal cells targeted the lateral, transient zone of PVT which contains fewer CR+ cells. Significant cortical inputs to the core region were only found in FoxP2 animals, which labels deep layer 6 cells. These results demonstrate that the PVT integrates excitatory and inhibitory information arising from distinct subcortical centers and that these subcortical inputs mainly target CR+ neurons. Cortical L5 inputs largely segregate from subcortical afferents and target a more lateral cell

population. In summary, the data show that cortical and subcortical information is process by distinct cell populations in the PVT.

**Disclosures: L. Biro:** None. **Z. Buday:** None. **K. Kóta:** None. **Á. Babiczky:** None. **F. Mátyás:** None. **L. Acsady:** None.

**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.08/FF21

**Topic:** F.03. Stress and the Brain

**Support:** Sigma Xi Grant Aid in Research
Biological Sciences Initiative

**Title:** The effects of inescapable stress on leukocyte subpopulations in male rats previously treated with Mycobacterium vaccae NCTC 11659

**Authors: *A. K. LEE**[1], J. R. MATNEY[1], S. N. BORDEN[1], X. CISNEROS[1], M. G. FRANK[1], A. S. MACDONALD[2], S. O. REBER[3], C. A. LOWRY[4];
[1]Univ. of Colorado At Boulder, Boulder, CO; [2]Univ. of Manchester, Manchester, United Kingdom; [3]Lab. for Mol. Psychosomatics, Univ. Clin. Ulm, Ulm, Germany; [4]Dept. of Integrative Physiol. and Ctr. for Neurosci., Univ. of Colorado Boulder, Boulder, CO

**Abstract:** Inappropriate inflammation has been linked to stress-related psychiatric disorders such as anxiety disorders, mood disorders, and posttraumatic stress disorder. Increasing evidence suggests that the microbiota, particularly a category of microorganisms referred to as “Old Friends”, is an important determinant of immunoregulation. However, how these “Old Friends” are able to exert their immunoregulatory effects is not fully understood. Subcutaneous (s.c.) injection of heat-inactivated *Mycobacterium vaccae* NCTC 11659, a saprophytic “Old Friend” from mud, has been shown to have a protective effect on anxiety- and depressive-like behaviors in several animal models of stress. For example, administration of *M. vaccae* prior to stress exposure has stress resilience effects in the juvenile social exploration test in male rats exposed to inescapable tail shock stress (IS) in a model of learned helplessness, but the mechanisms involved are not fully understood. Previous studies have shown that anxiety- and depressive-like behaviors are associated with an increase of circulating Ly6CHi inflammatory monocytes in mice. One hypothesis is that *M. vaccae* NCTC 11659 may be exerting its effects in part through its interaction with these inflammatory monocytes. This experiment characterized the effects of s.c. *M. vaccae* NCTC 11659 (three weekly s.c. injections of 0.1 mg of *M. vaccae* NCTC 11659 in 100 µl of sterile borate-buffered saline) or vehicle on leukocyte subpopulations after IS or home cage control conditions ($n$ = 6-8 per group) in rats using a nine-color flow cytometry immunophenotyping panel that identified neutrophils, inflammatory and anti-inflammatory monocytes, natural killer cells, B cells, and CD4+ and CD8+ T cells. Compared to home cage

controls, IS increased the relative abundance of neutrophils but decreased the relative abundance of lymphocytes in peripheral blood six hours after IS. Additionally, IS increased the relative abundance of inflammatory monocytes, suggesting that the stress-induced effects of IS may be due in part to increases in the relative abundance of inflammatory monocytes. These novel data are consistent with the hypothesis that inflammatory monocytes are involved in the pathogenesis of stress-induced anxiety-like defensive behavioral responses. Prior administration of *M. vaccae* NCTC 11659 not only attenuated the increase of inflammatory monocytes, but caused an increase of NK cells. Our data suggest that *M. vaccae* NCTC 11659 may exert its immunomodulatory effects in part by reducing the number of inflammatory monocytes.

**Disclosures:** **A.K. Lee:** None. **J.R. Matney:** None. **S.N. Borden:** None. **X. Cisneros:** None. **M.G. Frank:** None. **A.S. MacDonald:** F. Consulting Fees (e.g., advisory boards); Immodulon Therapeutics, Ltd. **S.O. Reber:** None. **C.A. Lowry:** F. Consulting Fees (e.g., advisory boards); Immodulon Therapeutics, Ltd.

**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.09/FF22

**Topic:** F.03. Stress and the Brain

**Support:** R01MH127835

**Title:** Threat generalization and context discrimination after Single-Prolonged Stress

**Authors: *R. K. PARIKH**[1], M. A. SMAIL[1], J. B. CHAMBERS[1], K. DAMA[2], J. P. HERMAN[1]; [1]Univ. of Cincinnati, Cincinnati, OH; [2]The Ohio State Univ., Columbus, OH

**Abstract:** Post Traumatic Stress Disorder (PTSD) is a human disorder with a variety of long term effects, such as extinction and fear memory deficits. An animal model commonly used to model symptoms of fear in rodents is the Single-Prolonged Stress (SPS) model. Previously, it has been shown that SPS modulates activity in many stress related brain regions, such as the basolateral amygdala (BLA) and the bed nucleus of the stria terminalis (BST). It has also been shown that the BST plays an important role in the generalization of a threat. The BLA appears to have a stronger effect on imminent fear, while the BST appears to have a stronger effect on contextual sustained fear over longer periods of time. Here we investigated the effects of SPS on threat generalization and on activation in the BST (anterolateral and anteroventral subnuclei) and BLA, via c-fos staining. After acquiring animals with either an imminent (1 min) or delayed (9 min) shock, we tested them by placing them in a novel context with no shock to determine the degree to which they generalized a threat. The animals were euthanized 90 minutes after testing to allow for the quantification of activated c-fos. There appears to be decreased freezing in the 1-minute shock control animals on testing day compared to the 9-minute shock control animals, suggesting less generalization of threat, just with a different shock time. Further analysis will

determine molecular and behavioral differences between groups as we examine effects of both shock time and stress. Understanding the role of SPS in threat generalization will help us better understand potential mechanisms of stress processing and the long-term effects of post-traumatic stress.

**Disclosures: R.K. Parikh:** None. **M.A. Smail:** None. **J.B. Chambers:** None. **K. Dama:** None. **J.P. Herman:** None.

**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.10/FF23

**Topic:** F.03. Stress and the Brain

**Title:** Early stress impacts conditioned place preference and alters dorsal raphe orexin innervation in adolescent male hamsters

**Authors: *K. MORAN**[1], Y. DELVILLE[2];
[2]Psychology, [1]Univ. of Texas, Austin, Austin, TX

**Abstract:** Early life stress is a consistent predictor of later-life obesity. In hamsters, a two-week exposure to chronic social stress in adolescence causes a consistent 10% increase in weight gain, food intake, and body fat. To examine possible differences in food-related motivation, we tested hamsters under a food hoarding and food conditioned place preference (CPP) task. Male Golden Hamsters (n=10/group) were exposed to a resident-intruder or clean cage control condition for 20 minutes per day from postnatal day 28 (P28) to P42 (early- to mid-adolescence) and a CPP protocol from P38 to P42. On food hoarding training days, stressed and non-stressed subjects both spent more time in the food wing, yet stressed subjects collected twice as much food as controls. However, on the CPP day, while control hamsters spent more time in the food-associated wing, stressed subjects spent equal amounts of time in all wings. CPP differences are likely associated with a form of frustration associated with lack of expected rewarding stimuli. In a previous study, similarly stressed hamsters spent less time in areas previously associated with food rewards under unexpectedly long delays. Brains of subjects (n=10/group) were immunocytochemically labeled for orexin and images of regions related to motivation and metabolism were taken. Axonal innervation was quantified via counting intersections with a cycloid grid and transformed to surface area. Of regions quantified, none showed group differences in innervation. However, orexin innervation in the dorsal raphe nucleus (DR) displayed a positive correlation with body weight, rate of weight gain, fat mass, and food hoarded in stressed subjects and no such relationship in controls, with the difference being statistically significant. These findings may reflect stress-sensitive mechanisms in orexin's influence on serotonergic activity related to feeding, arousal, and energy expenditure that alter lifelong metabolic processes.

**Disclosures:** **K. Moran:** None. **Y. Delville:** None.

**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.11/FF24

**Topic:** F.03. Stress and the Brain

**Support:** R01MH122742
T32GM008688
T32NS105602

**Title:** Transient elevation of corticosterone supports psilocybin's anxiolytic effects

**Authors: *N. JONES**, J. RAZIDLO, Z. ZAHID, L. WAGNER, C. WENTHUR;
Univ. of Wisconsin, Madison, WI

**Abstract:** Investigation into the clinical use of the serotonin (5HT-2A) receptor agonist psilocybin in conjunction with psychotherapy has shown promising therapeutic results in the treatment of psychiatric disorders. Correlations between drug-induced cortisol elevation and treatment outcomes have been reported for human studies during psilocybin-assisted psychotherapy; however, the mechanistic relationship between psychedelic-associated alterations in plasma corticosterone (CORT) responses and the anxiolytic efficacy remains unclear. A time course for psilocybin to induce anxiolysis in the absence of any intervention was conducted with C57/Bl6 mice and LC-MS/MS. Serum samples tested at doses of 0.3, 1, and 3 mg/kg found peak concentrations at 15 min post-injection. In the open field test 15 minutes post-injection, mice that received 3mg/kg psilocybin demonstrated decreased center time, while the 0.3 mg/kg exhibited a dose-dependent increase. However, at 4 h post-injection, the reverse was found, in that 0.3mg/kg psilocybin decreased center time. This dose-dependent interaction correlates with psilocybin-induced increases in CORT levels that peak at 15 min and return to baseline by 4 h. In addition, the non-hallucinogenic compound lisuride and NDMAR antagonist ketamine were used and demonstrated a transient increase in corticosterone concentrations at 15 min and returned to baseline by 4 h. When tested in the novelty suppressed feeding test, all three compounds reduced the latency to feed 4 h post-injection. Although following exposure to chronic oral CORT and when administered the glucocorticoid antagonist, mifepristone, both psilocybin and ketamine lost this anxiolytic effect. Chronic exposure to CORT and mifepristone suppressed the psilocybin-induced stress response and increased CORT. At a dose of 3 mg/kg IP psilocybin was found to have post-acute anxiolytic-like effects that were not altered by pretreatment with the non-hallucinogenic 5-HT2AR antagonist, ketanserin. In addition, psilocybin has demonstrated sustained antidepressant effects following a single administration, although the neuronal population supporting these effects remains unresolved. Given that changes in neural activation patterns may be directly relevant to psilocybin’s anxiolytic efficacy, whole brain clearing and cFos staining was used to quantify changes in neural activation. Cleared whole-brains were

imaged, cell-counted, registration to the Alan Brain Atlas as preliminary data. These results suggest that psilocybin-induced stress response, and increased plasma CORT levels, are supportive of the observed anxiolytic effects.

**Disclosures:** **N. Jones:** None. **J. Razidlo:** None. **Z. Zahid:** None. **L. Wagner:** None. **C. Wenthur:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Psilera and Mike/Mary Shannon. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Psilera Inc. Other; Usona.

**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.12/FF25

**Topic:** F.03. Stress and the Brain

**Support:** JSPS KAKENHI Grant JP17J02160
JSPS KAKENHI Grant JP18K06011

**Title:** Is delayed nest-building behavior in mice exposed to acute social defeat stress associated with arginine vasopressin?

**Authors: *H. OTABI**[1,2,3], M. SATO[2,3], H. IKEDA[3], A. TOYODA[3,2];
[1]Kagawa Univ., Kagawa, Japan; [2]United Grad. Sch. of Agr. Sci., Tokyo Univ. of Agr. and Technol., Tokyo, Japan; [3]Col. of Agr., Ibaraki Univ., Ibaraki, Japan

**Abstract:** In mice exposed to social defeat stress, nest-building behavior is delayed (Otabi et al., Behav Processes., 2016; 2017), but the underlying mechanism remains unclear. Reportedly, the activation of arginine vasopressin (AVP) neurons in the hypothalamic paraventricular nucleus inhibits nest building (Bendesky et al., Nature., 2017). In this study, we focused on the relationship between hypothalamic AVP, which is involved in nest building, and stress regulation, to identify the mechanism responsible for delayed nest building in mice exposed to acute social defeat stress (ASDS). We hypothesized that ASDS induces the activation of hypothalamic AVP neurons and elevates AVP concentration, which, in turn, inhibits nest building. Eight-week-old male C57BL/6J mice (B6) were subjected to physical stress for 5 min by aggressive ICR male mice. Subsequently, the B6 mice were transferred to the opposite side of the transparent partition in the same cage to induce psychological stress (Otabi et al., Behav Processes., 2017). Blood and hypothalamus were collected 1, 6, and 24 hours after ASDS, and AVP concentration was measured using EIA. After injecting (i.p. or i.c.v.) a vasopressin 1b receptor antagonist (SSR149415; SSR), the mice were exposed to ASDS, and the nest-building behavior was assessed using the nest score (Deacon, Nat Protoc., 2006). Hypothalamic AVP levels decreased 24 hours after ASDS exposure compared to that in the control group, but no

significant differences were observed at other time points between the groups. Neither i.p. nor i.c.v. administration of SSR could restore or improve the delayed nest-building behavior in ASDS-exposed mice. These findings suggest that hypothalamic and peripheral AVP may not be involved in nest-building deficits observed in ASDS-exposed mice. Our results differ from previous findings reported by Bendesky et al. (Nature., 2017). The decrease in AVP protein expression in the hypothalamus 24 hours after ASDS may be considered a novel finding; however, further investigations are necessary to ascertain the physiological significance of this phenomenon.

**Disclosures: H. Otabi:** None. **M. Sato:** None. **H. Ikeda:** None. **A. Toyoda:** None.

**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.13/GG1

**Topic:** F.03. Stress and the Brain

**Support:** Merit Award #BX004693

**Title:** The role of discrete brain regions in the therapeutic effects of 5-HT4 agonists on dopamine system function in rodent models that display psychosis-like pathology

**Authors: *O. YANG**[1], S. M. PEREZ[2], D. J. LODGE[3];
[1]Univ. of Texas Hlth. Sci. Ctr. San Antonio, San Antonio, TX; [2]Pharmacol., [3]UTHSCSA, UTHSCSA, San Antonio, TX

**Abstract:** Symptoms of psychosis are observed in numerous neuropsychiatric disorders including PTSD and schizophrenia and are thought to be driven by aberrant dopamine transmission in mesolimbic brain regions. Earlier work has revealed a key circuit that modulates dopamine activity in the ventral tegmental area (VTA) that includes the ventral hippocampus (vHipp), paraventricular nucleus of the thalamus (PVT), nucleus accumbens (NAc), and ventral pallidum (VP). Dysfunction at any of these brain regions can lead to disinhibition of VTA dopaminergic neurons, resulting in psychosis-like symptoms. The 5-hydroxytrptamine 4 (5-HT4) receptor is highly expressed in some of these brain regions and is being examined as a potential therapy for depression and anxiety. Given this, we believe it may also have utility in treating symptoms of psychosis. In this study, we used two different rodent models (MAM and two-day foot shock) that display psychosis-like symptomatology to investigate the role of 5-HT4 receptors in the regulation of dopamine neuron activity. We performed electrophysiological recordings in the VTA of rats and found elevated levels of spontaneously active dopamine neurons in our models used to study psychosis. Interestingly, the systemic administration of BIMU8 (1 mg/kg i.p.), a selective 5-HT4 receptor agonist, was able to reverse aberrant dopamine system function in both models. Furthermore, intracranial injections of BIMU8 (7.5 ug) into the NAc were also able to normalize dopamine system function, suggesting that 5-HT4 receptors in

the NAc are mediating this effect. Taken together, the results of this study suggest that 5-HT4 receptors may be involved in the regulation of VTA dopamine transmission under pathological states and could be a potential therapeutic target for disorders where symptoms of psychosis are present.

**Disclosures: O. Yang:** None. **S.M. Perez:** None. **D.J. Lodge:** None.

**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.14/GG2

**Topic:** F.03. Stress and the Brain

**Support:** FORDECYT-PRONACES/3203/2021

**Title:** Construction of a Potential Suicide-Related miRNA-mRNA Regulatory Network: Molecular signatures

**Authors: *K. M. LÓPEZ**[1], C. A. ZABALA[2], H. M. RIVERA[3], M. E. ROJAS[1], G. PÉREZ[4], J. L. CORTEZ[5], L. E. GÓMEZ[7], J. M. CHIN CHAN[6], E. BAUTISTA RODRÍGUEZ[1];
[1]Univ. Popular Autónoma del Estado de Puebla, Puebla, Mexico; [2]Grupo de Investigación en Genética Animal, Univ. Nacional de Colombia, Bogotá, Colombia; [3]Dept. de Estudios Interdisciplinarios, Univ. de Tolima, Tolima, Colombia; [4]Inst. Nacional de Psiquiatría "Dr. Ramón de la Fuente Muñiz", México City, Mexico; [6]Facultad de Ciencias Químico Biológicas, [5]Univ. Autónoma de Campeche, Campeche, Mexico; [7]Hosp. Psiquiátrico "Dr. Rafael Serrano", Puebla, Mexico

**Abstract:** Suicide is the fourth leading cause of death among young people aged 15 to 19 worldwide (OMS, 2019). The etiology of suicidal behavior is complex and multifactorial; psychiatric illnesses have been correlated with suicide. Mann et al. (1999) found that approximately 95% of suicide victims had a mental illness such as depression, bipolar disorder, etc. From the neurobiological point of view, a model of diathesis or predisposition has been proposed with stressors of daily life and pathophysiological factors, such as aggressive and impulsive personality traits, which trigger suicidal crises independently of psychiatric disorders (Nugent et al., 2019). Although these findings have contributed to explaining the pathophysiology of suicidal behavior, much remains to be discerned about the molecular mechanisms, especially in aspects of gene regulation induced by miRNAs.Therefore, in this study, we examined differentially expressed miRNAs and mRNAs in brain tissue from suicide victims and brain tissues from healthy individuals by extracting four Gene Expression Omnibus (GEO) datasets. The first analysis consisted of extracting the differential expression profile of miRNAs (GSE344120, GDE101521), were we found 23 differentially expressed miRNAs from suicide victims versus healthy individuals, 5 of these miRNAs (miR-17-5p, miR-20a, miR-155, miR-181a y miR-497) were previously associated with suicide and suicide behavior. We found

18 miRNAs downregulated in both datasets and 5 miRNAs upregulated. In addition, the expression profile of mRNA (GSE66937, and GSE101521) was obtained, finding 6 mRNAs differentially expressed, NFKBIA, SVIL, C1QA, ITGA2B, RBP1and CD59, we carried out the search for the miRNAs that regulate these mRNAs, finding that NFKBIA and CD59 are regulated with 7 miRNAs that we found differentialy expressed. In both cases, with the differences in expression profiles, a gene regulation network model was created (transcription factors and mRNA-targets) generated by SAM and confirmed by LIMMA. Finally, an analysis of functional enrichment by KEGG signaling pathways and biological processes by Gene Ontology (GO) was performed.

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**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.15/GG3

**Topic:** F.03. Stress and the Brain

**Support:** Vulnerable Brain Project (vbp.life)
James S. McDonnell Foundation
NIH grant TL1TR001447

**Title:** Absence of association between gut microbiota composition and individual cortisol responses to physical stress in healthy humans

**Authors: *J. P. OYARZUN**[1], T. M. KUNTZ[2], C. HUTTENHOWER[2], J. E. LEDOUX[3], E. A. PHELPS[1,2,3];
[1]Harvard Univ., Cambridge, MA; [2]Biostatistics, Harvard T.H. Chan Sch. of Publ. Hlth., Boston, MA; [3]Ctr. for Neural Sci., New York Univ., New york, NY

**Abstract:** Rodent studies have demonstrated that the gut microbiota shapes the development and responsiveness of the Hypothalamic Pituitary Axis (HPA). In humans, the administration of probiotics has been shown to improve stress responses, and the composition of the gut microbiota in infants has been linked to cortisol reactivity following exposure to stressors. Furthermore, individuals with anxiety who also exhibit HPA dysregulation have been found to have a distinct gut microbiota signature compared to healthy controls. However, there are currently no examinations of the connection between the composition of the gut microbiota in its homeostatic state and HPA reactivity in healthy adults. Our study (N=134) investigated whether variations in individuals' cortisol responses following a physical stressor (the Cold Pressor Task) were associated with differences in their microbiota composition. Analysis using PERMANOVA on Weighted UniFrac at both the species and genus levels did not reveal any significant

association between cortisol increase after stress and gut microbiota composition. Even though our sample was more than double the size of previous studies in humans, it is possible we are underpowered to detect such an effect. Alternatively, the observed associations between the gut microbiome and HPA axis activity in previous human studies may depend on specific population characteristics. To explore these possibilities, further research could offer valuable insights.

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**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.16/GG4

**Topic:** F.03. Stress and the Brain

**Support:** UNAM-PAPIT IG200121
CONAHCYT CF-2023-G-243

**Title:** Vasopressin circuit atypical innervation in basal forebrain of C58/J mice

**Authors: *O. HERNANDEZ PEREZ**[1], L. ZHANG[2];
[1]Physiol., Fac. of Medicine, UNAM, Mexico city, Mexico; [2]Physiol., Natl. Autonomous Univ. of Mexico, Mexico City, Mexico

**Abstract:** The C58/J inbred mouse strain has a behavioral profile that reflects the core symptoms of autism, including deficits in sociability, impaired communication, and overt motor stereotypies. These mice have been extensively studied in the context of social behavior and communication deficits. However, little is known about any anomaly in neuropeptide circuitry in these animals. Recently, neuropeptide arginine vasopressin (AVP) ascending circuits' role on behavior has been extensively studied. AVP influences several emotional disturbances such as anxiety, depression, exaggerated fear, etc., as well as promotes social interaction upon homeostatic challenges.To evaluate the influences of AVP in autism spectrum disorder (ASD) behavioral expression in C58/J mice, we first mapped the AVP expression in the whole brain of C58/J, comparing it with C57BL mice. Using immunohistochemistry, we found potentiated peptide and atypical innervation patterns in the nucleus basalis of Meynert (NBM), zona incerta, the bed nucleus of stria terminals, and the medial amygdala. Interestingly, we observed the innervation of NBM showed an orthogonal migration/innervation pattern of AVP cells and fiber from the paraventricular nucleus of the hypothalamus.

**Disclosures: O. Hernandez Perez:** None. **L. Zhang:** None.

**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.17/GG5

**Topic:** F.03. Stress and the Brain

**Support:** R37 DA033396/DA/NIDA NIH HHS/United States

**Title:** The role of Claustrum Dynorphin/KOR signaling involved in stress-induced binge eating

**Authors: *S. E. MAR**[1], J. CHEN[2], L. MANGIERI[2], S. C. PIANTADOSI[2], P. DAVIS[2], B. LAND[3], M. R. BRUCHAS[2];
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**Abstract:** In humans, stress is often correlated with a change in eating behaviors, increasing caloric intake in many individuals. The underlying hormonal and neural signaling pathways behind stress-induced binge-eating behaviors have yet to be determined. This is largely due to the lack of validated behavioral models linking stress and binge eating despite the common patterns observed in humans. Here, we focused on the development and characterization of a stress-induced binge-eating mice model using forced swim stress and a highly palatable diet (HPD). We found that stressed mice consumed significantly more HPD relative to their baseline consumption using both swim stress and foot shock. In contrast, this binge-eating phenotype was not seen in a calorically demanding wheel-running assay. The dynorphin (dyn)/kappa opioid receptor (KOR) neuropeptide system is well known for playing a crucial role in mediating the dysphoric/anhedonic aspects of stress. We thus investigated the potential role of KOR in our behavioral model. Injection of the KOR selective agonist U50,488H (5 mg/kg) resulted in an increase in HPD consumption while the KOR selective antagonists aticaprant (5 mg/kg) and norBNI (10 mg/kg) blocked forced-swim induced binge-eating behaviors, indicating a prominent role for dynorphin/KOR signaling in this behavior. We used cFos mapping to determine brain regions of interest and found that the claustrum (CLS), a subcortical structure with highly abundant expression of KORs, shows significant increases in cFos expression after stress and/or HPD exposure. Local norBNI injected in the claustrum recapitulated systemic injection, blocking stress-induced increases in HPD intake. Fiber photometry recordings in the claustrum using the fluorescent dynorphin sensor kLight revealed elevated dynorphin release. Injection of retrograde virus rAAV-DIO-GFP and slice imaging in Pdyn-Cre mice traced these dynorphin releasing neurons back to the insular cortex. We also injected CaMKII-GCaMP into the claustrum and observed elevated activity matched to HPD feeding onsets. Finally, we stimulated synaptic terminals in the claustrum of the insular cortex Pdyn-Cre neurons infected with AAV-DIO-Chrimson and found a small increase in HPD consumption. Our results demonstrate a robust behavioral model for stress-induced binge eating. Furthermore, the dynorphin/KOR system in the CLS appears to be important for this elevation in HPD intake after stress. This assay will allow researchers to begin to study the underlying hormonal and neural determinants behind stress-induced binge-eating behaviors mimicking eating disorders in humans.

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**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.18/GG6

**Topic:** F.03. Stress and the Brain

**Title:** Pharmacologic hyperreactivity of kappa opioid receptors in periaqueductal gray matter during alcohol withdrawal syndrome in rats

**Authors: *P. LEÓN**[1], H. SANCHEZ-CASTILLO[1], B. MARICHAL-CANCINO[2], A. MIRANDA-PAEZ[3];
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**Abstract:** Periaqueductal gray matter (PAG) is one of the brain regions rich in kappa-opioid receptors (KOR). KOR in PAG mediates behavioral responses related to pain integration, and panic response, among others. Its participation in the addiction phenomena has been poorly studied. In this research, its function during alcohol withdrawal on anxiety-type behaviors and alcohol relapse was explored. Juvenile male Wistar rats were unexposed (A-naïve group) or exposed to alcohol for 5 weeks and then restricted (A-withdrawal group). Posteriorly, animals received intra dorsal-PAG (D-PAG) injections of vehicle (10% DMSO), salvinorin A (SAL-A; 0.1 nmol/0.5 µl) a potent selective agonist of KOR, or 2-Methyl-N-((2'-(pyrrolidin-1-ylsulfonyl)biphenyl-4-yl)methyl)propan-1-amine (PF-04455242; 0.1 nmol/0.5 µl) a novel highly selective KOR-antagonist. Subsequently, defensive burying behavior (DBB) paradigm and alcohol preference was evaluated. SAL-A markedly increased burying time, height of bedding, alcohol consumption and preference in A-withdrawal, while in A-naïve rats it slightly increased height of bedding. PF-04455242 decreased both burying and immobility duration, whereas increases latency to burying, frequency of rearing, and the number of stretches attends besides decreased alcohol intake and preference in A-withdrawal rats. In general, stimulation/blockade of KORs in A-withdrawal animals exert higher responses compared to alcohol-naïve ones. SAL-A produced anxiety-like behaviors and increased alcohol intake/preference, especially/solely in alcohol-withdrawal, while PF-04455242 augmented exploration with no effects on alcohol intake/preference. Our findings suggest hyperreactivity of the KORs in PAG during alcohol-withdrawal.

**Disclosures: P. León:** None. **H. Sanchez-Castillo:** None. **B. Marichal-Cancino:** None. **A. Miranda-Paez:** None.

**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.19/GG7

**Topic:** F.03. Stress and the Brain

**Title:** Dissociation of hedonic reaction and motivation after chronic stress exposure

**Authors: *Y. B. VIDAL-DE LA O**[1], P. TORRES-CARRILLO[2], K. VALENCIA[3], D. B. PAZ-TREJO[4], H. SANCHEZ-CASTILLO[5];
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**Abstract:** Stress is considered the main predisposing factor for the development of depression-like behaviors. Motivational deficits and anhedonia are one of the most affected areas. However, the differential impact depending on the kind of stressor and the sex of the subjects are not considered in many studies. For all this, the main goal of this research was to analyze the hedonic reaction and motivation in an animal model of unpredictable chronic stress and social isolation in male and female Wistar rats. Particularly, we used chronic unpredictable stress battery (CUSB) and post-weaning social isolation (PWSI). We evaluated the motivation with the test of progressive ratio (PR) and the conditioned place preference test (CPPT). Additionally, we use the saccharine preference test (SPT) and free choice task (FCT) for the hedonic reaction. We found a sex divergence in males with CUSB and PWSI induced anhedonia. This was observed through the decrease in saccharine and evaporated milk consumption in SPT and FCT tests. However, the females with CUSB don't decrease their consumption. On the other side, PWSI increments the intake of evaporated milk. Additionally, the males with CUSB had a minor breaking point, increased latency to retrieve a reward and more consumption of water in the PR test. All those results support the motivational impairment with CUSB, while PWSI has not. This dissociation was not found in females. In conclusion, the dissociation of hedonic reaction and motivation is sex and stressor-type dependent. The above demonstrate how important are considerate stressor type and sex in depression and stress models.

**Disclosures: Y.B. Vidal-De La O:** None. **P. Torres-Carrillo:** None. **K. Valencia:** None. **D.B. Paz-Trejo:** None. **H. Sanchez-Castillo:** None.

**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.20/GG8

**Topic:** F.03. Stress and the Brain

**Support:** DGAPA IN208722

**Title:** Characterization of the stress response in Octopus maya: Behavioral changes produced by acute white bright light exposure.

**Authors: *D. GONZÁLEZ-NAVARRETE**[1], N. TRUJILLO-GUTIÉRREZ[2], F. SÁNCHEZ-FLORES[2], F. AYALA-GUERRERO[2], D. B. PAZ-TREJO[3], H. SÁNCHEZ CASTILLO[2]; [1]Univ. Nacional Autónoma De México, Ciudad de México, Mexico; [2]Univ. Nacional Autónoma de México, Ciudad de México, Mexico; [3]Univ. Nacional Autonoma de Mexico, Mexico City, Mexico

**Abstract:** In the environment, the organisms are exposed to stressful stimuli that require behavioral and physiological adaptation. In this fashion, the stress response becomes extremely important, because its activation allows the individuals to increase the probability of survival. Unfortunately, the evaluation of the stress response in octopuses is one poorly studied area. So, the knowledge about the effects of environmental stressors that may have on behavior and cognition remains unclear. Octopuses have been shown to be inactive inside a den throughout the day, avoiding light so as not to be detected by predators. For this reason, we propose the white bright light as environmental stressor in order to study the stress response in octopus. So, the main goal of this study was to evaluate the behavioral changes in *O. maya* produced by an acute stress exposure of bright light. Four individuals of *Octopus maya* were used and maintained in tanks with a closed circulation seawater system in a 12:12 LD cycle. They were divided into 2 groups: a group exposed to a low intensity red light 30lx (control) and a group exposed to white bright light 130lx (experimental). The experiment was performed in an experimental tank (60x40x30cm) and the exposure to the white bright light was made for 12 hours (08:00-20:00). We evaluated the time and frequency of rest and locomotion behavior in octopus. The obtained results showed that the exposure to acute stress (12h) decreased the time and frequency of locomotion behaviors (climbing and jet propulsion) and has no effects in crawling and rest behaviors in comparison with the control group in *O. maya.* Those results suggest that the use of the white bright light as an environmental stressor triggers the stress response and provoke a change in the behavior of the octopus. This is good precedent for future research in this field and encourage to pay more attention to the environmental stimuli that we use in the laboratory conditions.

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**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.21/GG9

**Topic:** F.03. Stress and the Brain

**Support:** DGAPA-PAPIIT IN208722
PAPIME PE306318

**Title:** Modulation of mGluR5 on depression-like, anxiety-like behaviors and spatial memory induced by predator stress exposure.

**Authors: *P. TORRES-CARRILLO**[1], A. C. ARMAS-SÁNCHEZ[2], Y. B. VIDAL-DE LA O[2], P. VÁZQUEZ-LEÓN[2], D. B. PAZ-TREJO[2], L. D. OCHOA-DE LA PAZ[2], H. SANCHEZ-CASTILLO[2];
[1]Univ. Nacional Autónoma De México, Ciudad de Mexico, Mexico; [2]Univ. Nacional Autónoma de México, Ciudad de México, Mexico

**Abstract:** The prevalence in the development of stress-related disorders is higher in women than in men. However, findings on the underlying mechanisms as well as the evaluation of pharmacological treatments of stress-related disorders have been reported mostly in males. Exploration of biological systems of stress-induced depression-like and anxiety-like behaviors in females is necessary to have a better understanding of the effects of stress, prevalence, symptomatology, prognosis, and treatment of stress-related disorders in females. On the other hand, the involvement of the glutamatergic system has been an alternative in the explanation of the mechanisms that modulate the stress response. For example, it has been reported that the administration of MTEP, an inhibitor of mGluR5 receptors, has antidepressant and anxiolytic effects. Exposure to stress increases the expression of mGluR5 receptors in the prefrontal cortex, amygdala, and hippocampus, so these receptors may be associated with stress-induced depression-like, anxiety-like, and fear-like behavior. However, no studies have been conducted on the effects of MTEP administration under stress conditions in females. The goal was to evaluate the intracerebroventricular administration of MTEP in females after exposure to predator stress. Female Wistar rats (12 weeks old) were used. Subjects were divided into a vehicle group and 3 different concentrations of MTEP groups (1ug/ul, 5ug/ul, and 10ug/ul), half of the subjects were stressed, and the other half were kept in non-stressed conditions (n=10 per group). After stress exposure, they were evaluated with the Barnes maze test, open field test, and forced swim test. The results found in the Barnes maze were stress decreases escape latency and the number of errors in the training phase, however, in the reversal training phase stress increases escape latency and the number of errors, and this is improved with the administration of the highest concentration of MTEP (10 ug/ul) but not with the lowest concentration of MTEP (1ug/ul). In the open field test stress decreased the time spent in the center of the arena and increased the time spent immobile in the forced swim test, while the stress-exposed group administered the highest concentration of MTEP (10ug/ul) increased the time spent in the center and decreased the time spent immobile, but not with the lowest concentration of MTEP (1ug/ul). The observed effects of MTEP administration can reverse stress-induced effects, indicating an important role of mGluR5 receptors in modulating stress in females.

**Disclosures: P. Torres-Carrillo:** None. **A.C. Armas-Sánchez:** None. **Y.B. Vidal-De La O:** None. **P. Vázquez-León:** None. **D.B. Paz-Trejo:** None. **L.D. Ochoa-De La Paz:** None. **H. Sanchez-Castillo:** None.

**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.22/GG10

**Topic:** F.03. Stress and the Brain

**Support:** Falk Transformational Award (CN)

**Title:** Using single-cell RNAseq to identify novel target genes and pathways in stress responses and antidepressant action

**Authors: *S. AZAM**[1,2], B. BIGIO[2], N. JOHN[1], Y. SAGI[1,2], C. KHOSLA[4,5,6], C. NASCA[3,1,2]; [1]Ctr. for Dementia Res., Nathan Kline Inst., Orangeburg, NY; [2]Dept. of Psychiatry, [3]Dept. of Neurosci. and Physiol., NYU Sch. of Med., New York, NY; [4]Dept. of Chem. Engin., [5]Dept. of Chem., [6]Sarafan ChEM-H, Stanford Univ., California, CA

**Abstract: Using single-cell RNAseq to identify novel target genes and pathways in stress responses and antidepressant action**
Authors: Shofiul Azam, Betty Bigio, Neelu John, Yotam Sagi, Chaitan Khosla, Carla Nasca
The ventral hippocampus is emerging as a central hub and critical for the regulation of the responses to chronic stress and antidepressant drugs. Our and other laboratories showed transcriptome-wide alterations in the ventral hippocampus after chronic stress, with a specificity of changes in the ventral dentate gyrus (vDG), and that administration of acetylcarnitine (LAC) rapidly ameliorate stress-induced effects on these transcriptomic profiles. Here, we used 10X Genomics droplet-based technology to perform Single Cell RNAseq (scRNAseq) for identifying the effects of chronic stress and antidepressant drugs of interest on each cell type of the ventral hippocampus, including the vDG. Our preliminary data showed a robust dissociation of single nuclei from the ventral hippocampus as shown by the integrity of nuclei as well as the absence of nuclear aggregates and cellular debris. Next, using 10x Genomics Chromium Controller System and Illumina Novaseq6000, we obtained high-quality reads (95% of reads with quality>= Q30) with a sequencing depth of 37300 reads/nucleus from a total of 10411 nuclei/sample. Our preliminary scRNAseq data and advanced bioinformatic analysis also showed ~20 distinct cell-type clusters based on their expression patterns. Ongoing experiments are aimed at identifying gene expression profiles of specific cells that are known targets of chronic stress and antidepressant drugs. The single-cell approach here serves as a model for identifying new markers and underlying mechanisms of predisposition to diseases and antidepressant action that may be useful in translational research.

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**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.23/GG11

**Topic:** F.03. Stress and the Brain

**Support:** Hope for Depression Research Foundation

**Title:** Exosomes and glutamatergic function in the response to chronic stress

**Authors: *H. KRONMAN**[1], A. SINGH[2], D. ZELLI[3], P. DEANGELIS[5], J. DOBBIN[4], B. BIGIO[7], C. NASCA[7,8,6,2];
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**Abstract:** Exosome-mediated transfer of functional biological material is a recent addition to fundamental regulatory mechanisms that contribute to the modulation of brain plasticity. Preclinical studies have shown that the release of exosomes is regulated by glutamatergic neurotransmission, and that patients suffering from major depressive disorder show increased peripheral levels of neuronal exosomes. Here, we provide an RNA-seq roadmap for two stress-sensitive brain areas, the ventral dentate gyrus (vDG) and basolateral amygdala (BLA), capturing transcriptome-wide alterations in these regions after 21 days of chronic restraint stress (CRS), a paradigm which has previously been shown to result in glutamate overflow as compared to non-stressed controls. Advanced bioinformatic analyses showed 395 differentially expressed genes in the vDG and 115 in the BLA (FDR < 0.15, |log(fold change)| ≥ 1.3). 43 of these overlap, and are related to exosomal processes across the two interconnected brain regions. Ongoing analyses are aimed at testing the role of the metabotropic glutamate receptor-2 (mGlu2), a key inhibitor of spontaneous glutamate release, in the regulation of exosome signaling in the CRS paradigm. These findings provide a starting point for the creation of a novel mechanistic framework for brain plasticity in the response to chronic stress.

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**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.24/GG12

**Topic:** F.03. Stress and the Brain

**Support:** NIH Grant R56MH125895

**Title:** Continuous high-throughput automated home-cage system to characterize the complex behavioral responses to stress

**Authors: *Y. SAGI**[1,2], N. JOHN[1], S. AZAM[1,2], B. BIGIO[2], C. NASCA[3,2,1];
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**Abstract:** Stress is a primary risk factor for the development of mood and cognitive disorders. Prior work showed that 2 hours of daily restraint for 21 days leads to pronounced behavioral deficits, and that administration of the novel epigenetic modulator of glutamatergic function Acetyl-L-carnitine (LAC) rapidly ameliorates the effects of stress. At present, technologies for monitoring the progression of the effects of stress on complex behaviors are not available. Here, we assessed the behavioral effects of sub-chronic (7 and 14 days) and chronic (21 days) restraint stress on emotional and cognitive outcomes using traditional tests and compared them with new data that we generated using a cutting-edge, automated, high-throughput behavioral system for continuous recording from mice in their home cages to capture the progression of stress responses over time. We also linked these behavioral phenotypes to underlying changes in signaling pathway in specific brain regions. Our data show a progressive manifestation of stress-induced behavioral abnormalities, with specific behavioral deficits occurring at 21 days only (n=12/group, $p<0.05$). Ongoing work is aimed at testing the effects of administration of LAC and standard antidepressant drugs in ameliorating the effects of stress on brain plasticity using this novel home-cage recording system. The continuous, automated, home-cage behavioral recording is particularly important because it will help us to obtain integrated measures of multi-faceted domains altered by chronic stress.

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**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.25/GG13

**Topic:** F.03. Stress and the Brain

**Support:** Whitehall Foundation
Brain and Behavior Research Foundation

**Title:** Role of a nucleus ambiguus peptidergic system in regulating stress and cardiac function

**Authors: *S. SHETTY**[1], P. HUYNH[2], S. DUESMAN[3], C. MCALPINE[2], A. K. RAJBHANDARI[4];
[1]Neurosci., Icahn Sch. of Med. At Mount Sinai Grad. Training Program In Neurosci., New York, NY; [2]Cardiovasc. Res. Inst., [3]Psychiatry, Icahn Sch. of Med. at Mount Sinai, New York, NY; [4]Psychiatry, Icahn Sch. of Med. At Mount Sinai, New York, NY

**Abstract:** Research has shown a strong association between post-traumatic stress disorder (PTSD) and cardiovascular dysfunctions. However, the mechanisms linking PTSD and cardiac functions are poorly understood. Previous studies have elucidated that the brainstem contains

centers that regulate both stress response and cardiac functions. The nucleus ambiguus (NA) in the brainstem sends direct neuronal projections to the heart and is a primary parasympathetic regulator. While several neuropeptides are expressed in the NA, studies have shown that pituitary adenylate cyclase-activating polypeptide (PACAP) is highly expressed in the NA. PACAP regulates central and peripheral stress responses. Thus, we hypothesized that NA-PACAP neurons play a role in coordinating stress-related fear responses and cardiac function. To test this hypothesis, we injected AAV-expressing designer receptors (DREADDs) to allow activation/inhibition of NA-PACAP neurons in Adycap1-Cre mice (~n=5/group). We used stress-enhanced fear learning (SEFL) to assess fear expression, and open-field light gradient task to measure anxiety-like phenotype. We also employed telemetry in conjunction with behavioral analysis to capture real-time cardiac changes. At the end of the study, we collected the brain to check for viral placement and blood and bone marrow to analyze immune cell expression using spectral flow cytometry. Our results demonstrated that NA-PACAP chemogenetic activation with clozapine increased freezing behavior, blood monocytosis, and myeloid hematopoiesis in stressed mice, like unstimulated stressed mice. However, unstimulated and NAPACAP-activated stressed mice did not exhibit changes in heart rate deviation (HRD). This indicates that NA-PACAP neurons are activated in response to stressors but do not influence associated cardiac functions. Chemogenetic inhibition of NA-PACAP alone in stressed mice increased freezing, blood monocytosis, and myeloid hematopoiesis in unstressed mice. Chemogenetic inhibition of NA-PACAP in stressed mice increased anxiety-like phenotype while lowering HRD, which indicates a reduction in parasympathetic activity or increased sympathetic dominance. Our results suggest that NA-PACAP inhibition may lead to a domination of sympathetic fear response, anxiety-like phenotype, and lower HRD. Thus, a genetic and cell-type specific regulation via the NA-PACAP pathway regulates stress-induced changes in behavior, immune cell trafficking, and cardiac function in stressed mice. Our results are relevant for understanding the mechanisms linking stressors, behavioral outcomes, and cardiovascular changes as observed in PTSD.

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**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.26/GG14

**Topic:** F.03. Stress and the Brain

**Support:** The Friedman Brain Institute
Brain and Body Research Foundation
Whitehall Foundation

**Title:** Selective stimulation of the vagal nodose ganglion neurons alter stress related behaviors and cardiorespiratory functions

**Authors: *S. J. DUESMAN**[1], S. SHETTY[2], B. KELLER[1], A. K. RAJBHANDARI[1]; [1]Psychiatry, Icahn Sch. of Med. at Mount Sinai, NEW YORK, NY; [2]Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY

**Abstract:** Post-traumatic stress disorder (PTSD) has a long-lasting adverse impact on brain and body health and behavior. Preclinical research suggests that broad stimulation of the vagus nerve, a major parasympathetic pathway, is effective for counteracting some PTSD symptoms in humans. However, the specific cell populations that drive this effect are unknown. Research suggests that pituitary adenylate cyclase-activating polypeptide (PACAP), which is expressed in the vagal nodose ganglion (NDG), is integrally involved in stress mechanisms. Thus, we hypothesized that selective stimulation of the PACAPergic pathway stemming from the NDG is sufficient to reduce behavioral and physiological effects of stressors in mice. To achieve this, we selectively stimulated PACAPergic neurons in the NDG and studied the effect on contextual fear, cardiorespiratory function, and anxiety-like behavior in mice. We micro-infused separate cohorts of *Adcyap1-2A-Cre* mice with AAV8-hSyn-DIO-rM3D(Gs)-mCherry into the NDG and utilized the designer drug clozapine to chemogenetically activate PACAPergic neurons. We sacrificed the first cohort (n=2) and performed cFos staining in brain areas known to regulate stress. The second cohort (n=25) was tested for stress-enhanced fear learning (SEFL) and contextual fear extinction. In a subset of mice (n=12) we also performed non-invasive pulse oximetry during behavior to acquire heart rate deviation (HRD) data. Finally, we assessed anxiety-like behavior in the elevated plus maze (EPM) in a subset of mice (n=13). Following chemogenetic activation of PACAPergic neurons in the NDG we observed an increase in cFos+ cells in the nucleus of the solitary tract, locus coeruleus, central amygdala, and paraventricular nucleus of the hypothalamus. NDG PACAPergic stimulation did not affect freezing behavior during SEFL. However, following contextual fear extinction in stressed animals paired with chemogenetic PACAPergic stimulation in the NDG, we observed a significant reduction in freezing behavior compared to stressed AAV8-hSyn-mCherry controls. PACAPergic stimulation in stressed mice also resulted in a rescue of HRD prior to extinction and an increase in open arm exploration in the EPM compared to controls. Our results indicate selective chemogenetic stimulation of NDG PACAPergic neurons alters neural activity in brain areas involved in stress regulation and coordinates peripheral cardiorespiratory signals with central responses to stressors. This research highlights the need to interrogate brain and body interactions via genetically defined vagal neurons to advance novel therapeutics for stress-related conditions like PTSD.

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**Poster**

**PSTR036. Stress-Modulated Pathways: Other Pathways**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR036.27/GG15

**Topic:** F.03. Stress and the Brain

**Support:** W911NF-13-1-0376
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W81XWH-10-1-0021
W81XWH09-2-0044
W81XWH-14-1-0043
W81XWH-10-2-0072
W81XWH-13-1-0071

**Title:** Divergent pathway activation patterns in the recent versus chronic post-traumatic stress disorder

**Authors: *S. MUHIE**[1], A. GAUTAM[2], B. MISGANAW[2], R. YANG[2], K. SWIFT[2], S. H. MELLON[3], A. HOKE[4], J. FLORY[5], B. DAIGLE[6], P. CONSORTIUM[7], L. HOOD[8], F. DOYLE III[9], O. WOLKOWITZ[10], C. MARMAR[11], K. J. RESSLER[12], R. YEHUDA[13], R. HAMMAMIEH[2], M. JETT[14];
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**Abstract:** Metabolomics, proteomics and DNA methylome assays, when done in tandem from the same blood sample and analyzed together, offer an opportunity to evaluate the molecular basis of post-traumatic stress disorder (PTSD) course and pathogenesis. We performed separate metabolomics, proteomics, and DNA methylome assays on blood samples from two well-characterized cohorts of 159 active duty male participants with relatively recent onset PTSD (< 1.5 years) and 300 male veterans with chronic PTSD (> 7 years). Analyses of the multi-omics datasets from these two independent cohorts were used to identify convergent and distinct molecular profiles that might constitute potential signatures of severity and progression of PTSD and its comorbid conditions. Molecular signatures indicative of homeostatic processes such as signaling and metabolic pathways involved in cellular remodeling, neurogenesis, molecular safeguards against oxidative stress, metabolism of polyunsaturated fatty acids, regulation of normal immune response, post-transcriptional regulation, cellular maintenance and markers of longevity were significantly activated in the active duty participants with recent PTSD. In contrast, we observed significantly altered multimodal molecular signatures associated with chronic inflammation, neurodegeneration, cardiovascular and metabolic disorders, and cellular attritions in the veterans with chronic PTSD. Activation status of signaling and metabolic pathways at the early and late timepoints of PTSD demonstrated the differential molecular changes related to homeostatic processes at its recent and multi-system syndromes at its chronic phase. Molecular alterations in the recent PTSD seem to indicate some sort of recalibration or compensatory response, possibly directed in mitigating the pathological trajectory of the disorder.

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**Poster**

**PSTR037. Oscillations During Sleep and Rest: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR037.01/GG16

**Topic:** B.07. Network Interactions

**Support:** MNESYS – A multiscale integrated approach to the study of the nervous system in health and disease

**Title:** Different brain synchronisation in deep sleep and wake

**Authors: *M. CANU**[1], M. ROASCIO[1], L. CHIARELLA[1,2], L. DI TULLIO[1,2], S. WANG[3,4,6,7], R. MAI[8], F. CARDINALE[8], L. NOBILI[1,2], J. PALVA[3,5], G. ARNULFO[1,3];
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**Abstract:** During the day, the brain receives exogenous and endogenous stimuli and stored information are consolidated during the night (Fattinger, et al. 2017). Deepest sleep (N3) is an important sleep stage of our brain involved in memory function, synaptic and network plasticity (Geva-Sagiv, et al. 2023). Phase synchrony represents a mechanism for enabling efficient large-scale neural communication (Nayak, et al. 2017). This work aims to study how sleep affects phase synchrony in humans.We computed the Phase Locking Value (PLV) between cortical regions outside the epileptogenic zone between 2 and 250Hz to evaluate the phase synchronisation LFP signal. We acquired an average of 10 minutes of spontaneous activity in wake condition (eyes-closed) and during the N3 from 36 drug-resistant focal epileptic patients undergoing invasive presurgical evaluations. We excluded inter-ictal epileptic spikes from the analyses as they might inflate instantaneous phase synchronisation.Compared to wake, in N3 sleep the global level of phase synchronisation was significantly higher ($p<0.05$ Kruskal-Wallis with Benjamini/Hochberg correction) in the sigma band (10-15 Hz). We found statistical differences in four frequency bands: theta (6-9 Hz), sigma (10-15 Hz), beta (25-35 Hz), and high-frequencies oscillations (150-190 Hz). The largest difference occurs in the sigma band where the Default Mode Network, Dorsal Attention Network(DAN), Temporal Parietal and Control systems are more tightly coupled than in wake condition. DAN shows high values of synchronisation in theta band with limbic, Salience/ Ventral Attention network, and Somatomotor networks in wake in comparison with N3. The main difference in high-frequencies oscillations is a higher connection between Temporal Parietal system with Control and Default

Mode in wake than N3. In Beta band, Temporal Parietal system shows a tight synchronization with Control A in wake while in N3 this network has a larger difference is with Dorsal Attention Network and Limbic system.These results suggest that during the night the brain regions show high synchronisation in the sigma frequency range with respect to the wake stage. This band of frequencies is typically associated with the sleep spindle of thalamus-cortical activity that supports memory consolidation through the synchronisation of large cortical areas (Lindemann et al. 2016). Nayak, et al. 2017, with a EEG study, reported an increase of synchrony in beta band from wake to N3. This could argue the synchronisation of Temporal Parietal system with Limbic system and DNA network of our results in this frequency band.

**Disclosures:** **M. Canu:** None. **M. Roascio:** None. **L. Chiarella:** None. **L. Di Tullio:** None. **S. Wang:** None. **R. Mai:** None. **F. Cardinale:** None. **L. Nobili:** None. **J. Palva:** None. **G. Arnulfo:** None.

**Poster**

**PSTR037. Oscillations During Sleep and Rest: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR037.02/GG17

**Topic:** F.07. Biological Rhythms and Sleep

**Support:** CONACYT Grant 263377
Hospital General de México Grant DI/12/403/04/003,
PAPIIT-UNAM Grants IA208018, IA100522

**Title:** Sleep spindles and sigma band phase synchrony in the human amygdala-hippocampal-neocortical circuit

**Authors: I. ABREGO-ISLAS**[1], C. J. MONTES-RODRÍGUEZ[1], M. CORSI-CABRERA[2], F. VELASCO[3], A. L. VELASCO[3], *Z. MUNOZ-TORRES[4,5];
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**Abstract:** Functional relationships between the hippocampus and amygdala are detected during the encoding, retrieval, and consolidation of emotional memories. Previous research has highlighted electrophysiological signatures of the hippocampus in establishing communication through synchrony during sleep as a potential mechanism for memory consolidation. Sleep spindles are transient activities in the sigma range (9-16 Hz) occurring during N2 and N3 of non-rapid eye movement (NREM) sleep that reach cortico-thalamic neurons and seem to participate in long-term memory. We explored and compared the basic properties of sleep spindles and

sigma activity among the amygdala, hippocampus, and neocortex to shed light on the potential mechanisms of NREM sleep underlying emotional processing. Simultaneous to intracranial (iEEG) recordings, standard all-night polysomnography, including 17 EEG derivations, were performed on 4 patients with intractable epilepsy candidates for neurosurgery. iEEG electrodes were placed stereotaxically using the occipital parasagittal technique in the amygdala-hippocampal axis. Recordings took place in a soundproof room in the Neurology and Neurosurgery Ward of the Hospital General de México after the Research and Ethics Committee approved the study and all patients signed the informed consent. Sleep spindles of N2 were automatically detected. We found shorter spindles in subcortical than cortical regions. The properties of slow spindles (9-12 Hz) are masked by fast spindles (12-16 Hz) when analyzed together. Sigma power was significantly higher during N3 and N2 than during waking and REM sleep in the amygdala, but especially in the hippocampus, which shows higher power than the amygdala during slow and fast sleep spindles. Hippocampal-cortical synchrony in the sleep spindle frequencies was spread across the cortex, whereas the amygdala showed punctual higher synchronization with the temporal lobe. Nonsignificant changes in phase synchrony were observed between the amygdala and hippocampus across brain states. The dynamics of sleep spindles in a brain circuit that is involved in emotion and memory support the existence of a mechanism that depends on NREM sleep for the stabilization and refining of emotional memories.

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**Poster**

**PSTR037. Oscillations During Sleep and Rest: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR037.03/GG18

**Topic:** F.07. Biological Rhythms and Sleep

**Title:** Reconfiguration of brain networks during sleep supports sleep-dependent learning interactions

**Authors: *X. LI**[1], M. UJI[1], R. KATSUMATA[1,2], A. SAOTOME[1,3], S. ARITAKE[1,3], M. TAMAKI[1,4];
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**Abstract:** Sleep plays a pivotal role in learning and memory. Although the current understanding has been based primarily on research in a single memory system, another line of research has suggested that different memory systems interact when there is a common rule between them. It remains unclear whether sleep facilitates learning interactions, and if so how. Here, we investigated the effects of sleep on interactions of procedural and declarative memories and the neural basis. In Exp.1 (n=29), participants were trained on a motor sequence and a visual

memory task, which had the same or different sequence structures. Participants were retested on the tasks after an overnight sleep. A group of different subjects was trained and retested intervening a period of wakefulness. Motor task performance improved significantly after sleep, without sacrificing visual memory performance, only when the tasks shared a common sequence structure. No significant improvement was found after wakefulness. In Exp.2 (n=15), we investigated sleep spindle activity in the supplementary motor area (SMA), a core region for motor sequence learning, and connectivity between brain regions crucial for visual memory. After participants were trained on motor and visual tasks, they took a 90-min nap with polysomnography, then they were retested on the tasks after nap. Coherence analysis was performed on source-localized EEG data, time-locked to sleep spindles originating in the SMA, to investigate the connectivity between brain regions involved in motor and visual memory. Motor task performance improved significantly after nap only for the same-sequence group, replicating the results of Exp.1. We found significantly *smaller* coherence values between the SMA and the early visual areas and between the right hippocampus and anterior cingulate cortex (ACC) in the same than the different-sequence group. The coherence values between the ACC and the left hippocampus were *larger* in the same than the different-sequence group. These results suggest that sleep enhances learning interactions via reconfiguration of brain networks involved in procedural and declarative memory systems during sleep for facilitation of plasticity and sequence information transfer.

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**Poster**

**PSTR037. Oscillations During Sleep and Rest: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR037.04/Web Only

**Topic:** F.07. Biological Rhythms and Sleep

**Support:** (NSF/BMBF grant 01GQ1706)

**Title:** Stimulating the stimulated cortex - simultaneous acoustic and electric stimulation during slow wave sleep

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**Abstract:** Closed-loop acoustic stimulation (CLAS) enhances endogenous slow oscillations (SO) but has an inconsistent effect on memory formation. Anodal tDCS (atDCS) is associated with a modulation in cortical excitability possibly related to a shift in (noradrenergic) neuromodulation [1]. To investigate whether a different level of cortical excitability can impact

CLAS efficacy on electrophysiological and behavioral responses of memory consolidation and post-sleep encoding, we combined these two non-invasive stimulation techniques in a within-subject single blinded, pseudo-randomized study on healthy humans (N=24; 17 female; 18 - 30 years, 21.92±2.93, mean± SD). Subjects completed two sessions of nocturnal sleep undergoing either CLAS or CLAS and atDCS. Stimulations were applied during slow wave sleep. Memory consolidation was assessed by a non-sense word paired associate task (NSWP) and a figural paired-associate task, and post-sleep encoding by a word paired-associate task. Cognitive ability was determined in a separate session. Combined atDCS and CLAS did not affect behavioral performance overall. Retention performance on the NSWP task for individuals with higher cognitive ability was impaired in atDCS + CLAS as compared to CLAS alone ($p=0.016$; N=10; Student's t test), whereas individuals with lower cognitive ability showed no significant difference ($p=0.892$; N=8; Student's t test; $F(1,16)=19.809$, $p<0.001$ for the interaction Condition X Cognitive ability, N=18). In terms of electrophysiological data, atDCS+CLAS tended to enhance values reflecting the SO hyperpolarisation Down-state compared to CLAS alone over frontal areas ($p<0.05$; N=20, ANOVA). This increment in the hyperpolarizing phase may underlie the measured increment in SO duration ($p<0.05$; N=20; ANOVA). Interestingly, the increased SO hyperpolarization Down-state was more pronounced in the subgroup of individuals with higher cognitive ability ($p<0.05$; N=10; Fisher's LSD). Results support previous findings on the influence of trait-like cognitive abilities on the efficacy of non-invasive stimulation, and a potential influence of anodal tDCS on a homogenous subset of subjects. 1. Ngo H, Martinetz T, Born J, Mölle M (2013). Neuron 78: 545-553; Henin S, Borges H, Shankar A, et al, (2019). eNeuro 6(6): ENEURO.0306-19.2019; Adelhöfer, N. et al. (2019). Brain Structure and Function 224(3): 1291–1300.

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**Poster**

**PSTR037. Oscillations During Sleep and Rest: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR037.05/GG19

**Topic:** F.07. Biological Rhythms and Sleep

**Support:** HBHL, McGill University - A03-M18-22A
CMER-RNQ 13-14-011

**Title:** Slow spindle trains during daytime sleep are associated with declarative memory consolidation

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Sacré-Coeur De Montréal, Montreal, QC, Canada; [6]Univ. Paris-Saclay, France, Paris, France; [7]Neurol. and Neurosurg., McGill University, Montreal, Montreal, QC, Canada; [8]McConnell Brain Imaging Ctr., McConnell Brain Imaging Ctr., Westmount, QC, Canada

**Abstract:** Memory consolidation refers to the process whereby freshly encoded memories are strengthened and retained over time. There is ample evidence indicating that sleep facilitates the consolidation of both procedural and declarative memories. While memory traces are believed to be reactivated and reprocessed during non-rapid eye movement (NREM) sleep in synch with specific events, like slow waves and spindles, it is unclear whether similar mechanisms subserve consolidation of different memory types or not. We reported previously that procedural memory consolidation is related to spindles grouped in 'trains' (i.e., occurring less than 6 seconds apart). Here, we investigated whether the same holds for the consolidation of declarative memory by demonstrating that: (1) a 90-minute nap improves declarative memory consolidation and (2) sleep-related memory performance correlates with spindle train metric(s). In a mixed experimental design, participants were assigned to either nap (N=23; $m_{age}$=24.09 yrs.) or no-nap (N=15; $m_{age}$=25.47 yrs.) groups and were required to perform an object spatial location task in which participants learned locations of 36 images in a 6-by-6 matrix before and after sleep or an equivalent wake period, respectively. Parametric and non-parametric tests compared group differences in memory performance and its association with spindle train metrics (proportion of spindles in trains) for the nap group only. The mean percentage of fully consolidated items was significantly higher for the nap group (M = 84.27, SEM = 3.10) than the no-nap group (M = 75.83, SEM = 6.25); [t(36)=2.35. p=0.03]. Only 20% of participants had retest gains in the no-nap group, as compared to 65% in the nap condition [$\chi^2$ (df=1) = 7.45, p<0.001]. Furthermore, in the nap group, the memory performance correlated significantly and positively with the proportion of spindles clustered in slow trains recorded on the frontal (Fz) electrode (r=0.352, df=21, p = 0.05) and with the local spindle density on electrodes Pz and Fz (p = 0.03 and p = 0.05 respectively). Our results align with the literature indicating that a 90-minute nap improves declarative memory consolidation. This improvement is associated with NREM2 spindle train metrics, stating that clustering of spindles in trains or slow/fast spindles alone is not enough, however slow spindles clustered in trains recorded on the frontal (Fz) scalp electrode is important for declarative memory consolidation.

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**Poster**

**PSTR037. Oscillations During Sleep and Rest: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR037.06/GG20

**Topic:** F.07. Biological Rhythms and Sleep

**Title:** Frequency-based algorithm for sleep and wake detection

**Authors: *G. EYLON**[1], M. HACOHEN[2], I. DINSTEIN[3];
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**Abstract: Objectives**: To develop and test an automatic algorithm that can accurately identify sleep onset and final awakening from recordings obtained with clinical Polysomnography (PSG) systems while taking into account individual baseline differences. Such an algorithm is an essential first step for enabling large-scale research into the neurophysiology of sleep using large PSG databases.
**Background**: While neural activity patterns recorded by electroencephalogram (EEG) exhibit distinct differences during sleep and wake states, it is often difficult to identify transitions between sleep and wake states due to different artifacts and movement noises and because of heterogeneity in recorded brain activity across individuals. During wake states, EEG data is dominated by Beta (13-25 Hz) and Alpha (8 – 12 Hz) activity. In the transition to sleep Beta and Alpha waves gradually decrease in amplitude, and lower-frequencies in the Theta (4 – 8 Hz) and Delta (1-4 Hz) bands increase. However, large individual differences exist in the absolute baseline amplitudes of these different frequency bands.
**Design/Methods**: Data was obtained from The Simons Foundation Autism Research Initiative (SFARI) database and included 56 overnight PSG recordings from children with ASD (N = 26) and typically developing (TD) controls (N = 30). First, we calculated spectral power, variance, kurtosis, mobility, complexity, correlation between channels and amplitude range in 30 second epochs of the PSG. We excluded epochs with extreme values in any of these variables and identified sleep onset and final awakening using a combination of Alpha/Theta ratio, Alpha-Theta difference, Alpha amplitude, and Theta amplitude. Importantly, thresholds for all of these measures were individually defined/calibrated according to the baseline of each participant.
**Results**: Algorithm identified sleep onset and final awakening was compared to manual annotations according to American Academy of Sleep Medicine (AASM) guidelines. The algorithm estimates of sleep onset times did not differ significantly from manual annotations (mean bias = -6.1 min, $t(55) = 1.6$, $p = 0.1$). Similarly, the algorithm estimates of final awakening times did not differ significantly from manual annotations (mean bias = 6.6 min, $t(55) = -1.8$, $p = 0.08$).
**Conclusions**: The developed and implemented workflow provides a valuable method for cleaning and analyzing large datasets of PSG, opening the door to large scale studies of human neurophysiology of sleep.

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**Poster**

**PSTR037. Oscillations During Sleep and Rest: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR037.07/HH1

**Topic:** B.07. Network Interactions

**Title:** Exploring the Impact of EEG-gated transcutaneous auricular vagus nerve stimulation on brain Delta power during sleep.

**Authors: *A. ANZOLIN**[1], P. DAS[2], R. GARCIA[3], A. CHEN[2], A. GRAHL[1], S. ELLIS[1], P. L. PURDON[2], V. NAPADOW[1];
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**Abstract:** Transcutaneous auricular vagus nerve stimulation (taVNS) is a non-invasive neuromodulation technique that applies an electrical current to the auricular branch of the vagus nerve. We proposed an innovative approach combining taVNS and electroencephalography (EEG) in a closed loop to modulate Delta waves (0.5 - 4 Hz) during sleep. EEG Delta power is a well-studied neural marker of sleep and has been used to detect states and disorders of consciousness such as delirium, which is the most common neuropsychiatric disorder observed in hospitalized patients, especially the elderly, and is characterized by acute deficits in awareness, attention, and cognition. Our EEG-gated auricular vagal afferent nerve stimulation (EAVANS) approach delivers targeted stimulation during specific phases of the Delta rhythm, with the goal of enhancing arousal and reducing neuroinflammation, two contributing factors to delirium. We propose that Delta phase-specific taVNS could enhance arousal by activating ascending noradrenergic pathways via the nucleus tractus solitarius in the brainstem and potentially disrupting a cycle of Up/Down states. As Delta power also characterizes non-rapid eye movement sleep, we applied a prototype of EAVANS on healthy volunteers (N=7) during sleep to establish preliminary validation. We used a wireless EEG system to acquire neuroelectric signals and state space models to estimate instantaneous Delta phase. The stimulation was delivered when Delta phase was rising in the interval between $-\pi/2$ and 0 radians using custom-built electrodes placed within the cymba conchae of the ear. We found that Delta power decreased during EAVANS with moderate to large effect sizes ($\eta^2 = 0.65$) and that this reduction was greater compared to 1) absence of stimulation, 2) stimulation during descending Delta phase, and 3) control stimulation at sites not innervated by the auricular branch of the vagus nerve. Further validation of EAVANS in the peri-operative period is needed to target delirium. Given the lack of effective treatments for delirium, this novel non-pharmacological and non-invasive closed-loop neuromodulatory device could be used peri-operatively to prevent or treat patients at risk of developing delirium.

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**Poster**

**PSTR037. Oscillations During Sleep and Rest: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR037.08/HH2

**Topic:** B.07. Network Interactions

**Support:** National Center for Advancing Translational Sciences (NCATS) Grant #UL1TR001414
Pediatric Exercise and Genomics Research Center (PERC) Systems Biology Fund

**Title:** A sleepery slope: Inhibitory control in the child-adolescent transition is associated with power-law scaling in the NREM sleep electroencephalogram.

**Authors: *A. DAVE**[1], K. K. LUI[5], I. Y. CHEN[2], M. CHAPPEL-FARLEY[3], S. RADOM-AIZIK[4], R. M. BENCA[6], A. B. NEIKRUG[2], B. A. MANDER[2];
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**Abstract:** Structural changes emblematic of the developing brain, e.g., synaptic pruning and myelination, are theorized to impact sleep architecture, local sleep physiology, and sleep-dependent cognition. Conventional analyses of sleep in development, relying on absolute or relative power from electroencephalography (EEG) to capture the functional impact of sleep rhythms on cognition, have disregarded the 1/f EEG power law as "neural noise". However, evidence tying steepness (1/f exponent) and intercept (1/f offset) of the power law curve to excitatory-inhibitory balance and asynchronous population spiking in underlying neuronal populations necessitate a reexamination of developmental sleep EEG spectra. Here, 19 healthy children and adolescents (ages 11-17, 11 girls) underwent overnight polysomnography with 128 channel EEG. Inhibitory control was assessed following sleep using inhibition scaled score (ISS) on a Color Word Interference Test. Spectral parameterization (fooof) was applied to NREM multitaper absolute spectra (0.5-40Hz) to extricate oscillatory from aperiodic features (1/f exponent, 1/f offset, and residual oscillatory power). Topographical correlations between parameterized median NREM spectra, age and ISS were obtained with 5000-permutation threshold free cluster enhancement. Bootstrapped multiple regressions adjusting for age and sex modeled the association between ISS and parameterized neural spectra. Age showed widespread negative topographical correlations with broadband absolute spectral power, but these effects vanished in correlations with all oscillatory residuals except slow sigma (11-13Hz), which showed a modest negative trend over a central cluster. Remarkably, age also showed widespread negative associations with 1/f offset, while age and 1/f exponent showed a negative trend over central channels. ISS was not significantly correlated with absolute power or with oscillatory residuals in canonical bands but was strongly negatively associated with 1/f exponent in a bilateral parietal arc. The cluster average of exponents from this parietal association significantly predicted next day ISS performance, adjusting for age and sex ($B = 0.803$, $p = 0.013$). Broadband changes in developmental NREM spectra may therefore be driven by aperiodic rather than oscillatory activity, and developmental inhibitory control while awake may partly be explained (independent of age) by parietal excitatory-inhibitory balance during sleep. More broadly, aperiodic features may serve a complementary role to neural oscillations in balancing local and systemwide information processing demands to support cognition in this cohort.

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**Poster**

**PSTR037. Oscillations During Sleep and Rest: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR037.09/HH3

**Topic:** F.07. Biological Rhythms and Sleep

**Title:** Patterns of Activity in Deep Brain Nuclei During Sleep in Humans

**Authors: *S. SEYYED MOUSAVI**[1], S. JAVADZADEH NO[2], J. NATARAJ[3], J. MACLEAN[4], Y. SUN[3], T. D. SANGER[5];
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**Abstract:** The activity of deep brain regions in humans during sleep versus wakefulness has been a long-standing question in the field of sleep science. Previous studies on this topic have largely utilized electrophysiologic recordings of transgenic animals, which may not be completely comparable to activity in the human brain. Advances in modern techniques such as deep brain stimulation (DBS) have provided the opportunity for us to revisit this topic and study patterns of neural activity in sleep vs. wakefulness in humans. We first aim to examine how patterns of neural activity in human deep brain regions change during sleep stages compared to wakefulness using spike and spectral analyses. Secondly, we aim to investigate the structural origin of oscillations that contribute to characteristic activity of different sleep stages using coherence analysis. For this purpose, we utilized intracranial and electroencephalogram (EEG) data of three pediatric subjects who underwent a staged implantation of DBS electrodes. Up to 12 stereoelectroencephalography (sEEG) electrodes were implanted in potential DBS targets that include subthalamic nucleus (STN) and globus pallidus interna (GPi), in basal ganglia; ventral intermediate nucleus (VIM) and ventral anterior nucleus (VA) in thalamus; and pedunculopontine nucleus (PPN) in brainstem. Each implanted electrode has 10 microelectrode contacts that enable us to record neural activity. Spike analysis demonstrates that firing rates of all detected neurons decrease significantly in all recorded deep brain regions during sleep compared to wakefulness. Spectral and coherence analyses provide further explanation about the origin of sleep stages. Results from this and similar studies have the potential to improve our understanding of the mechanisms of sleep. This could provide valuable insight into the treatment of sleep disorders such as insomnia or hypersomnia.

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**Poster**

**PSTR037. Oscillations During Sleep and Rest: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR037.10/HH4

**Topic:** F.07. Biological Rhythms and Sleep

**Title:** Neural dynamics of mental imagery, visual perception, and REM sleep

**Authors: *G. VESS**[1], A. KVAVILASHVILI[1], M. R. WITCHER[2], S. VIJAYAN[3]; [1]Virginia Tech., Blacksburg, VA; [2]Virginia Tech. Sch. of Neurosci. and Carilion Clin., Roanoke, VA; [3]Virginia Tech. Sch. of Neurosci., Blacksburg, VA

**Abstract:** In order to better understand the functional role of rapid eye movement (REM) sleep, we need a deeper understanding of the differences between neural activity during REM sleep and while awake. Specifically, interest lies in the temporal directionality of communication and coupling in neural activity between different areas of the brain during REM sleep and awake activities. One theory suggests dreaming, which occurs predominantly during REM sleep, may be a rehearsal mechanism for humans to incorporate information learned during the day, reflecting the memory consolidation function of sleep. Both mental imagery and dreaming are internally generated percepts, while sensory processing is more externally generated, though similar neural regions are utilized. The difference in information flow between REM sleep, mental imagery, and stimuli perception may help us understand which regions of the brain and neural processes are key for the functional role REM sleep may serve. Participants with no history of neurological disorders provide electroencephalogram (EEG) data, while other participants provide intracranial data with electrodes surgically implanted as part of their epilepsy treatment plan. Both sets of human participants are monitored during visual stimuli processing, imagery, and REM sleep. The visual stimuli involve identifying clock angles. The imagery task involves imagining two clock times and comparing their angles after an auditory stimulus. Both of these are applied in random order across multiple trials before and after sleep for performance comparisons. Brain activity during sleep is recorded during an overnight stay. The intracranial participants provide data for internal structures of the brain with access to more localized results, such as more low frequency activity observed in the hippocampus during REM. Participants undergoing the study with conventional EEG give a better distributed image of the entire brain. Results from 17 EEG participants show clear differences in the spectral content of certain regions of the brain when comparing the average power differences between visual stimuli, imagery, and REM. In particular, there is more power frontally and centrally in the delta and theta frequency bands in REM compared to the other two tasks, while the power is higher in these bands occipitally in the visual perception task. Beyond a better understanding of the neural dynamics underlying mental imagery, visual perception, and REM sleep, these results may help to derive better brain machine interface algorithms and provide more insight into diseases associated with REM sleep problems, such as Parkinson's, narcolepsy, and depression.

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**Poster**

**PSTR037. Oscillations During Sleep and Rest: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR037.11/HH5

**Topic:** F.07. Biological Rhythms and Sleep

**Support:** NIH Grant R00-MH111748
Polish National Academy for Academic Exchange
PPN/BEK/2020/1/00094
U19NS128613
U19NS123717

**Title:** Elucidating the theta paradox: distinct spectral characteristics of cognitive- and drowsiness-related increases in midfrontal theta EEG activity

**Authors: *E. BELDZIK**[1,2], Z. YANG[2], S. WILLIAMS[2], L. LEWIS[1];
[1]MIT, Cambridge, MA; [2]Boston Univ., Boston, MA

**Abstract:** Increases in midfrontal theta (4-8 Hz) EEG power have been observed in two markedly different conditions: during high cognitive demand and in sleep. Previous work has shown that theta power was elevated during working memory or cognitive conflict tasks and was positively correlated to response time (RT). On the other hand, sleep restriction and mental fatigue caused widespread increases in frontocentral theta power, both during resting state and during task performance. Interestingly, these two similar in topography phenomena have contradictory interpretations: first, as a marker of cognitive control; and second, as local sleep waves in awake state, which reflect, a detrimental to cognition, homeostatic sleep pressure. In this study (N=22 subjects), we explored this paradox by implementing a psychomotor vigilance task in the overnight EEG study. Across the 12-hour sleep deprivation period, we investigated which EEG dynamics were linked to time-of-night and to task performance (assessed via RT). We applied a linear mixed-effect model incorporating both RT and time-of-night variables to pre-stimulus and post-stimulus time epochs for a logarithmically spread range of EEG frequencies in a trial-by-trial fashion. In line with previous literature, midfrontal theta increased after stimulus onset relative to pre-stimulus baseline and this activity showed positive correlations with RT with a peak at 4.3 Hz. Furthermore, the time-of-night effect revealed a persistent pre-stimulus increase in the theta band that peaks at 8 Hz. Therefore, these two phenomena, cognitive and drowsy theta, can be disentangled within the theta band by their distinct spectral characteristics. Our results suggest that these high and low theta frequencies reflect independent neural processes, which explain the so-called theta paradox, and shed new light on the cognitive relevance of these commonly reported brain signals. Furthermore, this work provides a basis for neuroimaging investigations of the neural circuit dynamics underlying these oscillatory patterns.

**Disclosures: E. Beldzik:** None. **Z. Yang:** None. **S. Williams:** None. **L. Lewis:** None.

**Poster**

**PSTR037. Oscillations During Sleep and Rest: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR037.12/HH6

**Topic:** F.07. Biological Rhythms and Sleep

**Support:** NARSAD Young Investigator Award
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1907 Trailblazer Award
U19NS128613
R01AG070135

**Title:** Predicting cerebrospinal fluid flow in the human brain using EEG dynamics

**Authors: *S. ANAKWE**[1], H. FISHER[1], S. WILLIAMS[1], L. P. L. JACOB[2], L. D. LEWIS[1];
[1]Boston University, MIT, Boston, MA; [2]Massachusetts Inst. of Techology, Cambridge, MA

**Abstract:** Cerebrospinal fluid (CSF) surrounds and cushions the brain while also clearing waste products. CSF flow pulses at high rates during sleep, suggesting that the brain maintains active control over fluid flow. Previous work has shown that neural activity is coupled to and modulates CSF flow, but the specific relationship between these two processes remains unclear. To investigate the influence of neural activity on CSF flow dynamics, we used a machine learning model to test which aspects of EEG dynamics can predict CSF flow in the human brain. We acquired electroencephalogram (EEG) recordings simultaneously with resting state fast functional magnetic resonance imaging (fMRI) for both healthy controls and patients with depression. Subjects were instructed to keep eyes closed and were allowed to sleep during the scan. We placed the imaging volume at the edge of the fourth ventricle to capture the CSF inflow signal (N=22 sessions; 15 subjects). The spectral power of CSF flow between 0.05Hz to 0.2Hz was estimated using a one-minute sliding window. EEG spectral power in these windows was estimated in the low delta, high delta, theta, beta, and alpha bands. We trained a random forest regression model to predict CSF power using EEG band power as features. 75% of the dataset (n=275 segments) was used as the training set, and 25% (n=92 segments) as the test set. We found that the predicted CSF power was significantly correlated with true CSF power (Pearson's r= 0.62, p= 9.0e-11), with an $R^2$ of 0.38. We next tested how modifying the EEG input features affected model performance. When EEG delta power was removed as a feature, the model fit quality decreased substantially ($R^2$ = 0.04) even though the predictions remained significantly correlated to the actual values (Pearson's r=0.35, p= 8.8e-4). We then ran the model with three features (low delta, high delta, and each of the other EEG bands), and found that the model fit was the highest ($R^2$=0.24) and the correlation was the strongest (Pearson's r=.50, p= 4.2e-7) when using theta and delta as inputs. Overall, the results demonstrate that a significant amount of the low-frequency cerebrospinal fluid signal during sleep can be predicted from neural activity, particularly EEG theta and delta bands. Understanding the coupling between neural activity and CSF dynamics may inform our understanding of disease states such as Alzheimer's disease where CSF flow is disrupted.

**Disclosures: S. Anakwe:** None. **H. Fisher:** None. **S. Williams:** None. **L.P.L. Jacob:** None. **L.D. Lewis:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property

rights/patent holder, excluding diversified mutual funds); Inventor on patent for MRI method for measuring CSF flow.

**Poster**

**PSTR037. Oscillations During Sleep and Rest: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR037.13/HH7

**Topic:** F.07. Biological Rhythms and Sleep

**Support:** mcknight scholar award
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U19NS128613
U19NS123717
NSF 1625552

**Title:** Uncovering coupled EEG-fMRI dynamics across arousal states with machine learning

**Authors: *L. P. L. JACOB**[1], S. M. BAILES[2], S. D. WILLIAMS[2], L. D. LEWIS[1];
[1]Massachusetts Inst. of Techology, Cambridge, MA; [2]Boston Univ., Boston, MA

**Abstract:** Simultaneous EEG-fMRI (electroencephalography and functional magnetic resonance imaging) combines the high temporal resolution of EEG with the high spatial resolution of fMRI, but their joint analysis is challenging. Traditional approaches convolve the EEG with a hemodynamic response function (HRF), but relationships that do not follow the HRF's assumptions may be missed. Therefore, as a data-driven alternative, we use linear machine learning to identify fMRI patterns that predict the simultaneous EEG. EEG and fast fMRI (TR=0.367 ms; 2.5mm isotropic voxels) were collected from subjects (n=21) resting with eyes closed, drifting in and out of sleep. Sequences of 60 TRs (~22s) of fMRI signals from 84 parcellated brain regions were input into a linear regression model with L2 regularization, trained with stochastic gradient descent to predict delta (1.2-4Hz) and alpha (9-12Hz) EEG power. Validation was conducted on a held-out subject. As control, fMRI data was circularly shifted by 2000 TRs (~740s) prior to training and validation, breaking the true relationship between EEG and fMRI. We found that both delta (r=.38 between predictions and truth; control r=.05, p<.001) and alpha (r=.30; control r=.05, p=.005) were predicted from fMRI. We then trained the model on subsets of parcellated regions (cortex, subcortex, and 'physiological' regions—global white matter, representing blood flow, and ventricles). Distinct groups were predictive of each EEG band, with cortex best for delta (r=.36, vs. r=.27 for alpha) and subcortex best for alpha (r=.39, vs. r=.23 for delta). Physiological regions only predicted delta (r=.21, vs. r=.07 for alpha), likely owing to the known coupling between delta and cerebrospinal fluid/hemodynamic oscillations. To identify unique contributions from neural (cortical/subcortical) fMRI areas, we trained the model to predict EEG from each neural region. For the delta model, given its coupling to physiology, we also included the physiological areas—prediction differences could thus highlight neural effects not captured by global hemodynamics. Results revealed relationships not

detected with conventional approaches: alpha was strongly predicted by dorsal striatum (r=.28; also predicted by thalamus at r=.29, though the latter is established in the literature), while delta favored a diffuse pattern across the frontal and cingulate cortices (r=.30), and the putamen (r=.33). Taken together, our results demonstrate that fMRI dynamics can predict EEG rhythms on out-of-sample subjects, highlight EEG-fMRI relationships that elude traditional analyses, and further our understanding of brain networks involved in arousal states.

**Disclosures:** **L.P.L. Jacob:** None. **S.M. Bailes:** None. **S.D. Williams:** None. **L.D. Lewis:** None.

**Poster**

**PSTR037. Oscillations During Sleep and Rest: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR037.14/HH8

**Topic:** F.07. Biological Rhythms and Sleep

**Support:** NIH Grant F31MH127916
Pew Biomedical Scholars
NIH Grant U19NS128613
Sloan Fellowship
Searle Scholar Award

**Title:** The relationship between behavior and fMRI dynamics in the thalamus is state dependent

**Authors: *B. SETZER**[1], C. STRINGER[2], L. D. LEWIS[3];
[1]Boston Univ., Boston, MA; [2]Janelia Res. Campus, Ashburn, VA; [3]MIT, Cambridge, MA

**Abstract:** In light sleep and drowsiness, blood oxygen level dependent (BOLD) signals throughout the brain exhibit low-frequency oscillations. Precisely how these dynamics are related to behavior is not well understood. The thalamus is a core structure comprised of sub-nuclei with diverse functional roles in cognition, which exhibit distinct activity patterns during awakening from sleep. However, it is unclear how thalamic activity is linked to the ongoing oscillatory global waves of BOLD activity that occur during light sleep. These waves are locked to changes in respiratory variation which is a marker of changing arousal state. Furthermore, wave peaks and troughs propagate across the brain, from unimodal (early sensory processing) to transmodal (higher-order cognition) regions, indicating that they have some functional and spatial structure. However, it is unknown how this oscillatory activity is linked to behavior, or what differences exist between waves. We used ultra-high field (7 Tesla) functional magnetic resonance imaging (fMRI) to capture high resolution (n=5 subjects, temporal resolution 247 ms, 2.5mm3 voxels) dynamics across the brain. Subjects performed a simple button pressing task to track behavioral state, and were also allowed to fall asleep inside the scanner. We then clustered BOLD activity across thalamic voxels using unsupervised machine learning. This analysis captured both how temporal dynamics vary across the thalamus spatially and between individual

waves in the oscillation. We identified two distinct clusters of thalamic activity dynamics: one with low-amplitude fast oscillations, and one with slower, larger oscillations. In addition, we found that thalamic activity was coupled to behavior in a state dependent manner, with changes of behavior occurring more strongly in specific clusters of thalamic dynamics during oscillation peaks. Overall, this study reveals functional differences in thalamic oscillatory activity linked to drowsiness and light sleep, and identifies distinct patterns for how thalamus is coupled to behavior depending on the current brain arousal state.

**Disclosures: B. Setzer:** None. **C. Stringer:** None. **L.D. Lewis:** None.

**Poster**

**PSTR037. Oscillations During Sleep and Rest: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR037.15/HH9

**Topic:** B.07. Network Interactions

**Support:** JST Moonshot R&D (JPMJMS2012)

**Title:** Potential electroencephalographic markers of relaxation state in healthy adults: a systematic review and meta-analysis

**Authors: *M. TAKEMI**[1], H. KURASHIKI[1], K. SUGIMOTO[2], Y. XU[3], K. AMANO[3]; [1]Grad. Sch. of Sci. and Technology, Keio Univ., Yokohama, Japan; [2]Fac. of Sci. and Engineering, Waseda Univ., Tokyo, Japan; [3]Grad. Sch. of Information Sci. and Technology, The Univ. of Tokyo, Tokyo, Japan

**Abstract:** The human electroencephalogram (EEG) consists of neural oscillations at different frequencies, including alpha oscillations (8-13 Hz) often associated with relaxation. However, the extent to which various EEG components, including alpha oscillations, reflect the level of relaxation remains uncertain. In this systematic review, we investigated studies concurrently measuring EEG and reference indices of relaxation in healthy adults and conducted meta-analyses to assess their correlation. A computerized search was performed using the Web of Science, Scopus, PubMed, JDreamIII, and Ichushi-Web to identify relevant studies published between January 1st, 1940, and January 14th, 2021. Two authors (HK and KS) independently identified eligible studies, extracted data, and conducted a risk of bias assessment following the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS). Meta-analyses were performed using a random-effects model and robust variance estimation, with Fisher's Z-transformed correlation coefficients as the dependent variable. Thirty-nine studies identified for the qualitative synthesis used a variety of relaxation measures. Some studies employed electrocardiographic indicators related to the parasympathetic nervous system activity, while others utilized subjective indicators obtained through questionnaires. Meta-analysis of 30 studies with low to moderate risk of bias showed no significant correlation between the intensity (i.e. power and amplitude) of alpha oscillations and reference relaxation indices (standardized mean

difference (SMD) = 0.14, 95% CI [-0.13-0.40]), but with the existence of moderate heterogeneity among the studies ($I^2$ = 46.4%). Subsequent subgroup meta-analyses for each group of sensors (e.g. frontopolar, frontal, central, parietal, occipital) revealed a strong positive correlation between relaxation indices and the intensity of alpha oscillations in the frontopolar region (SMD = 0.95, 95% CI [0.18-1.73]). A weak but significant correlation was also found in the frontal (SMD = 0.15, 95% CI [0.03-0.28]) and central regions (SMD = 0.24, 95% CI [0.10-0.38]). No significant correlation was found in the parietal and occipital regions. The other EEG frequencies were not correlated with relaxation indices. These findings suggest that the intensity of alpha oscillations may represent relaxation, but their relationship varies depending on the position of EEG measurements. It is also important to note that equating alpha oscillations solely with relaxation would be inappropriate, as their strength can fluctuate with sleepiness, fatigue, and attentional state.

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**Poster**

**PSTR038. Ingestion and Energy Balance: Neuropeptides and Hormonal Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR038.01/HH10

**Topic:** F.08. Food and Water Intake and Energy Balance

**Title:** Erbb4 in the paraventricular nucleus of the hypothalamus regulates energy expenditure

**Authors: *I. SANTIAGO**[1], F. LIU[3], H. WANG[2], E. P. ARZOLA[2], W.-C. XIONG[2], L. MEI[2]; [1]Dept. of Neurosciences, [2]Dept. of Neurosci., Case Western Reserve Univ., Cleveland, OH; [3]Augusta Univ., Augusta, GA

**Abstract:** In the United States, about a third of its population suffers from obesity, and the prevalence is higher in people which suffer from major depressive disorder. Previous, Genome-Wide Association Studies (GWAS) have identified the receptor tyrosine kinase ErbB4 as a risk gene for obesity and for major depression disorder. We show that ErbB4 is expressed in the paraventricular nucleus of the hypothalamus (PVH), a region known to regulate metabolism. To investigate whether ErbB4 in the PVH regulates weight gain, we deleted ErbB4 by injecting a Cre-expressing virus into the PVH and found that PVH ErbB4 deletion increased weight gain without altering food intake in male mice. Moreover, ErbB4 PVH deletion reduced nighttime locomotor activity and decreased intrascapular brown adipose tissue (iBAT) thermogenesis. We further show that deletion of ErbB4 in the PVH reduces O2 consumption, CO2 consumption and heat generation, indicating reduced energy expenditure. Immunostaining experiments show that ErbB4+ neurons in the PVH are positive for oxytocin (OXT) and ErbB4 PVH deletion reduces serum levels of OXT. Our data suggest that ErbB4 in the PVH neurons regulate metabolism by controlling OXT expression. To test this hypothesis, we characterized mice where ErbB4 was specifically mutated in OXT+ neurons. Mice With OXT ErbB4 deletion showed reductions in

energy expenditure, phenotypes similar to PVH ErbB4 deletion. Taken together, our data indicate that ErbB4 in the PVH regulates metabolism likely by controlling the expression of OXT, reveal a novel function of ErbB4 and provide insight into pathophysiological mechanisms of depression-associated obesity.

**Disclosures: I. Santiago:** None. **F. Liu:** None. **H. Wang:** None. **E.P. Arzola:** None. **W. Xiong:** None. **L. Mei:** None.

**Poster**

**PSTR038. Ingestion and Energy Balance: Neuropeptides and Hormonal Control**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR038.02/HH11

**Topic:** F.08. Food and Water Intake and Energy Balance

**Support:** Emmy Noether grant DFG AC 371/1-1
NeuroNex grant DFG AC 371/2-1

**Title:** Aminergic and peptidergic modulation of Insulin-Producing Cells in Drosophila

**Authors:** R. S. BISEN, M. HELD, M. ZANDAWALA, I. S. BALLES, S. HILPERT, F. MILANI, ***J. M. ACHE**;
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**Abstract:** Insulin signaling plays a key role in controlling metabolic homeostasis and is heavily implicated in processes underlying reproduction, aging, and stress resistance. Insulin-producing cells (IPCs) in *Drosophila* are functional analogues to mammalian pancreatic beta cells and produce different *Drosophila* insulin-like peptides (DILPs). DILP release is dependent on nutrient availability, and IPCs are hypothesized to sense glucose levels in the brain. Therefore, we performed an *in-vivo* electrophysiological characterization of nutrient sensing in IPCs. Our results demonstrate that the nutritional state strongly modulates IPC activity. In 24h starved flies, the IPCs were basically quiescent, while they were firing at about 1 Hz in flies fed *ad libitum*. Interestingly, while changes in the IPC activity remained negligible when we perfused high-glucose saline over the brain of starved flies, re-feeding flies with a high-glucose diet strongly increased the IPC activity. This was reminiscent of the incretin-effect described in humans and other mammals, where the ingestion of glucose leads to a significantly higher release of insulin as compared to intravenous application of glucose.Due to the central role of insulin in maintaining metabolic homeostasis, IPC activity needs to be continuously adjusted to ever-changing internal demands. This is achieved by inputs from modulatory neurons impinging on the IPC population. We capitalized on the genetic toolkit available in *Drosophila* to characterize the modulation of IPCs *in-vivo*. First, we mapped receptor expression profiles across the IPC population and found that these were strongly heterogeneous, with each IPC expressing different sets of modulator receptors. To assess the functional significance of these receptor profiles, we recorded IPC activity using *in-vivo* calcium imaging and patch clamp recordings while

optogenetically activating different populations of peptidergic and aminergic neurons. We identified several modulatory populations that were able to shift the IPC population activity towards a more excited or a more inhibited regime. Interestingly, activating specific modulatory populations had heterogeneous, sometimes antagonistic effects on individual IPCs, with some IPCs exhibiting inhibitory, and others excitatory responses. These heterogeneous inputs add another layer of complexity to the modulation of IPCs, since they permit a nuanced control of the IPC population activity. Our approaches provide new insights into the regulation of IPC activity by other modulatory systems, which enables fine-controlled insulin release across various internal and behavioral states.

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**Poster**

**PSTR038. Ingestion and Energy Balance: Neuropeptides and Hormonal Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR038.03/HH12

**Topic:** F.08. Food and Water Intake and Energy Balance

**Support:** R01DK131452

**Title:** Unexpected metabolic and behavioral changes caused by viral vectors expressing cre recombinase in the paraventricular hypothalamic nucleus

**Authors: *R. SAVANI**[1], L. WANG[1], H. KWON[2], Z. PANG[1];
[1]Neurosci., [2]Child Hlth. Inst. of NJ, New Brunswick, NJ

**Abstract:** The paraventricular hypothalamic nucleus (PVN) is known to secrete corticotropin-releasing factor (CRF), a neuropeptide that plays a crucial role in regulating the hypothalamic-pituitary-adrenal axis. Emerging evidence suggests that CRF plays physiological roles in behaviors beyond the neuroendocrine stress response, such as in immunity, wakefulness, and anxiety-like behaviors. To further assess the role of PVN-derived CRF in such diverse roles, we used a loss-of-function approach by stereotaxically injecting AAV-Cre recombinase in the PVN of adult male *Crh-flox* mice. As anticipated, we observe reduced plasma corticosterone levels compared to littermate GFP-injected male *Crh-flox* control mice. Intriguingly, these mice exhibited rapid weight gain and increased daily food intake. Glucose and insulin tolerance tests revealed elevated blood glucose levels in the Cre-injected *Crh-flox* mice. Additionally, using the CLAMS monitoring system, we noted reduced energy expenditure and locomotor activity in these mice. To assess behavioral implications, we subjected the Cre-injected Crh-flox mice to the open field and light-dark box tests, which revealed slightly elevated anxiety-like behaviors. In order to confirm that our results were due to genetic knockout and not a confounding effect, we decided to repeat these results on a wild-type genetic background. Unexpectedly, we found similar phenotypic alterations in adult wild-type mice stereotaxically injected with AAV-Cre at

the same concentration (>1x$10^{13}$ vg/mL) in the PVN, suggesting that our observations may not be attributable to the depletion of CRF. Cre-injected wild-type mice displayed increases in body weight and food intake, as well as elevated anxiety-like behaviors. To further probe the potential confounding effects of Cre recombinase, we then examined the PVN of *Crh-flox* mice using immunohistochemical markers for known peptides. With this, we observed decreased immunofluorescence of both CRF and oxytocin as compared to littermate controls, indicating Cre recombinase interactions with other PVN cell types. Together, these results identify viral vector-mediated Cre recombinase activity as a potential confound in studying hypothalamic regions like the PVN and highlight the need for comprehensive controls when studying adult conditional knockout mouse models.

**Disclosures:** **R. Savani:** None. **L. Wang:** None. **H. Kwon:** None. **Z. Pang:** None.

**Poster**

**PSTR038. Ingestion and Energy Balance: Neuropeptides and Hormonal Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR038.04

**Topic:** F.08. Food and Water Intake and Energy Balance

**Title:** Voluntary wheel running improves a high-fat diet-induced inflammation in hypothalamic arcuate nucleus and ventral tegmental area in male mice.

**Authors:** T. SASAKI, ***M. SUGIYAMA**, M. KUNO, H. TAKAGI, R. BANNO, H. ARIMA; Nagoya Univ. Grad. Sch. of Med., Nagoya, Japan

**Abstract:** We previously showed that a high-fat diet (HFD) induced inflammation in both the hypothalamic arcuate nucleus (ARC) and ventral tegmental area (VTA) in the brain of mice. It is shown that hypothalamic inflammation induced by HFD occurs prior to substantial body weight gain with glial cell activation, and that the inflammation causes resistance to leptin and insulin, resulting in impairment of energy homeostasis through increased food intake and decreased energy expenditure. In addition, HFD-induced inflammation with glial cell activation in the VTA is suggested to affect the function of dopaminergic neurons and cause abnormal eating behaviors accompanied by insulin resistance in the VTA. Although exercise therapy is well known to be important in the treatment of obesity, the impact of exercise on HFD-induced inflammation in those areas in the brain remains unclear. In the present study, we investigated the effects of voluntary exercise on HFD-induced inflammation in the ARC and VTA. We divided 8-week-old male C57BL/6J mice into four group; a chow-fed sedentary group (CD/EX- group), HFD-fed sedentary group (HFD/EX- group), a chow-fed exercise group (CD/EX+ group), HFD-fed exercise group (HFD/EX+ group). We used wireless running wheels for voluntary exercise. Four weeks after the start of the experiment, the ARC and VTA were dissected from mice. We evaluated the mRNA expressions of inflammation-related cytokines (TNFα, IL1β, IL6, IL10) and glial markers (Iba1, GFAP, CD80) in the ARC and VTA by quantitative real-time PCR. In both the ARC and VTA, the mRNA expressions of TNFα and CD80 (microglial M1 marker) in

HFD/EX- group were significantly higher than those in CD/EX-, CD/EX+ and HFD/EX+ groups. Of note, there were no significant differences in the expressions of TNFα and CD80 among the CD/EX-, CD/EX+ and HFD/EX+ groups. These results indicate that voluntary wheel running suppresses HFD-induced inflammation in the ARC and VTA. The decreased mRNA expressions of TNFα and CD80 in HFD/EX+ suggest that voluntary exercise may have an anti-inflammatory effect by suppressing the polarity change to M1-type microglia. Our data provide an insight into the mechanism by which voluntary exercise prevents HFD-induced obesity.

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**Poster**

**PSTR038. Ingestion and Energy Balance: Neuropeptides and Hormonal Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR038.05/HH13

**Topic:** F.08. Food and Water Intake and Energy Balance

**Support:** CIHR, FDN-147473

**Title:** The effects of fasting on insulin-induced long-term depression of glutamatergic projections to ventral tegmental area dopamine neurons from the pedunculopontine tegmental nucleus

**Authors: *D. NEYENS**[1], S. L. BORGLAND[2];
[1]Physiol. and Pharmacol., [2]Univ. of Calgary, Univ. of Calgary, Calgary, AB, Canada

**Abstract:** Dopamine neurons of the ventral tegmental area (VTA) confer salience, reward, and motivational properties to external and internal cues as they relate to appetitive and motivated behavior. Importantly, these neurons are sensitive to peptides that signal metabolic status, such as insulin. VTA insulin signaling decreases dopamine release and the contextual associations of palatable food and psychomotor responses to cocaine. Insulin in the VTA induces long-term depression (LTD) of glutamatergic projections to VTA dopamine neurons. The pedunculopontine tegmental nucleus (PPTg) is a region that encodes sensorimotor and reward-related stimuli and sends strong projections to the VTA and activation of its terminals in the VTA can increase dopamine release in the nucleus accumbens (NAc). Insulin in the VTA can suppress PPTg-evoked dopamine in the NAc. However, it is unknown if insulin regulates PPTg terminals in the VTA and how this changes with fluctuating or disrupted physiological insulin, as occurs with fasting. Here, we will use optogenetics and slice electrophysiology to stimulate PPTg glutamatergic projections to VTA dopamine neurons and measure changes in insulin-induced LTD with metabolic status. Male and female mice were given ad libitum access to standard chow and received bilateral injections of a viral construct containing ChR2 (AAV2 CamKII-hCHR2(H134R)-EYFP) into the PPTg. Activation of ChR2 with blue light (5 mW, 0.2 ms, 473 nm) in the presence of picrotoxin produced robust optically-evoked excitatory

postsynaptic currents (oEPSCs) from PPTg terminals in dopamine neurons recorded from horizontal VTA slices. Insulin induced LTD in compound PPTg oEPSCs, which were afterwards confirmed to contain both polysynaptic and monosynaptic input as determined by treatment with tetrodotoxin (TTX) and 4-aminopyridine (4-AP). Roughly 80% of PPTg oEPSCs to lateral VTA dopamine neurons contained monosynaptic input. Future experiments will test the hypothesis that VTA insulin sensitivity increases, and insulin-induced LTD of PPTg oEPSCs is stronger, following fasting.

**Disclosures: D. Neyens:** None. **S.L. Borgland:** None.

**Poster**

**PSTR038. Ingestion and Energy Balance: Neuropeptides and Hormonal Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR038.06/HH14

**Topic:** F.08. Food and Water Intake and Energy Balance

**Support:** NIDDK Grant 5R01DK103808-07
NIDDK Grant F31DK134157

**Title:** Defining the feeding behavior effects of endogenous neurotensin from LHA neurons and their projections

**Authors: *J. Y. RAMIREZ**[1], P. STUART-HURTADO[2], G. M. LEINNINGER[3];
[1]Neurosci., [2]Physiol., Michigan State Univ., EAST LANSING, MI; [3]Physiol., Michigan State Univ., East Lansing, MI

**Abstract:** Obesity affects >40% of the US population and is characterized by excessive food consumption and a sedentary lifestyle that causes weight gain. Yet, incomplete understanding of how the brain controls feeding and movement behaviors has hindered development of weight loss therapies. Experimentally activating lateral hypothalamic (LHA) neurons expressing neurotensin (LHANts neurons) transiently increases water intake and body weight, but over 24 hr it suppresses feeding and increases energy expenditure to promote weight loss. The weight reduction effects, but not the drinking, are mediated by Nts signaling via neurotensin receptor-1 (NtsR1), which is robustly expressed by dopamine neurons in the Ventral Tegmental Area (VTA). Intriguingly, there may be distinct subsets of LHANts neurons that project to different brain areas to mediate drinking vs. feeding suppression. We hypothesized that LHANts neurons projecting to the VTA promote weight loss but not drinking. To test this, we used optogenetics to activate all LHANts neurons or only the subset of neurons projecting from the LHA to the VTA and assessed how they modulate feeding, drinking, moving and body weight. We observed that acutely activating all LHANts neurons does not impact feeding, but increases drinking. Conversely, activating only the LHANts neurons that project to the VTA reduced feeding without invoking a drinking response. These data suggest that biasing LHANts neuronal signaling to the VTA may have potential to support weight loss behaviors. Going forward,

understanding how central Nts signaling regulates feeding vs. drinking could suggest new strategies to support weight loss and address the obesity epidemic.

**Disclosures:** **J.Y. Ramirez:** None. **P. Stuart-Hurtado:** None. **G.M. Leinninger:** None.

**Poster**

**PSTR038. Ingestion and Energy Balance: Neuropeptides and Hormonal Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR038.07/HH16

**Topic:** F.08. Food and Water Intake and Energy Balance

**Support:** Lefler Fellowship
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**Title:** Competition between all-or-none neuropeptide signals calibrates the rate of satiation

**Authors: *X. ZHANG**[1], A. KIM[1], J. MADARA[1], P. K. ZHU[1], L. F. CHRISTENSON[1], A. LUTAS[2,1], P. KALUGIN[1], A. PAL[3], Y. JIN[3], L. TIAN[3], B. B. LOWELL[1], M. L. ANDERMANN[1];
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**Abstract:** MC4R-expressing neurons in paraventricular hypothalamus ($PVH^{MC4R}$) are a critical circuit node through which hunger-promoting NPY and satiety-promoting αMSH peptides regulate energy balance. Receptors for these peptides regulate intracellular cAMP, but the second messenger's spatiotemporal dynamics and role in energy balance are controversial. We show that photostimulating AgRP or POMC axons in PVH triggers probabilistic, all-or-none, NPY-dependent cAMP decrements or αMSH-dependent cAMP increments in $PVH^{MC4R}$ neurons. We trace the unpredictability of cAMP signaling to stochastic and spatially restricted peptide release events. NPY and αMSH exhibit competitive effects on cAMP signals, as reflected by hunger-state-dependent differences in the amplitude and persistence of cAMP transients evoked by each peptide. During feeding, elevated αMSH release and suppressed NPY release cooperatively

sustain elevated cAMP in $PVH^{MC4R}$ neurons, potentiating feeding-related excitatory inputs and promoting satiation across minutes. This study highlights how state-dependent integration of opposing, quantal peptidergic events by a common biochemical target calibrates energy intake.

**Disclosures:** **X. Zhang:** None. **A. Kim:** None. **J. Madara:** None. **P.K. Zhu:** None. **L.F. Christenson:** None. **A. Lutas:** None. **P. Kalugin:** None. **A. Pal:** None. **Y. Jin:** None. **L. Tian:** None. **B.B. Lowell:** None. **M.L. Andermann:** None.

**Poster**

**PSTR038. Ingestion and Energy Balance: Neuropeptides and Hormonal Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR038.08/HH17

**Topic:** F.08. Food and Water Intake and Energy Balance

**Support:** NSERC Discovery Grant RGPIN-2017-06272 (MC)
NSERC-PGSD (MP)
NSERC-USRA (AS)
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**Title:** Melanin-concentrating hormone-mediated feeding in the lateral septum

**Authors: *M. A. PAYANT**[1], A. SHANKHATHEERTHA[2], P. A. MILLER[1], D. SPENCER[2], M. J. CHEE[1];
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**Abstract:** Melanin-concentrating hormone (MCH) is a neuropeptide produced in the lateral hypothalamus and is well-established to regulate feeding and energy balance. Intracerebroventricular administration of MCH increases feeding in male rodents, but the specific brain regions underlying the orexigenic effects of MCH are not well-defined. The lateral septum (LS) receives dense projections from MCH neurons, expresses the MCH receptor MCHR1, and is inhibited by MCH treatment. Interestingly, LS inhibition stimulates feeding, thus it may mediate the orexigenic actions of MCH. Here, we determined if MCH stimulates feeding via the LS and investigated the spatial relationship between MCH fibers and MCHR1 expression to elucidate how MCH transmission mediates feeding in the LS. We bilaterally infused MCH (2 μg) directly into the LS of male (N = 6) and female mice (N = 8) and found that MCH elicited a rapid and long-lasting 2-fold increase in chow feeding in male, but not female, mice. However, when fed a highly palatable high sugar diet, MCH infusion also increased feeding in female mice, but this effect in females was short-lived. Importantly, infusing the MCHR1 antagonist TC MCH-7c (2 μg) into the LS completely blocked the orexigenic actions of MCH regardless of diet, thus MCH-mediated feeding is MCHR1-dependent. To determine how MCH may reach MCHR1-expressing LS cells, which are marked by ciliary MCHR1 immunoreactivity, we immunolabeled LS cells using neuronal nuclear protein (NeuN) and performed dual-label

immunohistochemistry to define MCH-immunoreactive (MCH-ir) fibers and MCHR1-ir cilia on NeuN-labeled LS cells. We recently showed high spatial overlap between the distribution of MCH fibers and MCHR1-LS cells, but although MCH-ir fibers were adjacent to MCHR1-LS neurons, very few MCH-ir varicosities formed appositions at the cilium or soma of MCHR1- LS neurons. Therefore, MCH may travel across the extracellular space to reach its LS cell target. To determine if the LS cells that are innervated by nerve terminals from MCH neurons are also MCH-sensitive, we expressed an AAV encoding channelrhodopsin-mCherry in the hypothalamus of *Mch-cre* mice and performed whole-cell patch-clamp recordings from LS cells. About 38% of LS cells recorded received monosynaptic glutamatergic contacts from channelrhodopsin-expressing *Mch-cre* fibers, but the majority (80%) of these LS cells were not MCH-sensitive thus suggesting that MCH may act via volume transmission. Taken together, these findings indicated that MCH can stimulate feeding via the LS and suggested that MCH may diffuse proximally within the LS to regulate even those cells that are not immediately adjacent to MCH fibers.

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**Poster**

**PSTR038. Ingestion and Energy Balance: Neuropeptides and Hormonal Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR038.09/HH18

**Topic:** F.08. Food and Water Intake and Energy Balance

**Support:** NSF GFRP to KS
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Quebec Research Funds postdoctoral fellowship (315201) to LDS
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**Title:** Melanin-concentrating hormone-producing neurons in the zona incerta promote excessive consumption

**Authors: *K. SUBRAMANIAN**[1], Z. WANG[1], L. DECARIE-SPAIN[1], A. NOURBASH[1], A. KAO[1], M. KLUG[1], A. AHUJA[1], K. MCBURNETT[1], K. DONOHUE[1], A. CORTELLA[1], S. TERRILL[2], D. BURDAKOV[3], J. HAHN[1], D. HOLSCHNEIDER[1], S. KANOSKI[1];
[1]USC, Los Angeles, CA; [2]Carthage Col., Kenosha, WI; [3]ETH Zurich, Zurich, Switzerland

**Abstract:** Melanin-concentrating hormone (MCH) is a neuropeptide produced in the lateral hypothalamic area (LHA) and zona incerta (ZI) that promotes food intake. The LHA and ZI are dissociated anatomically and functionally, yet the distinct roles of these two populations of MCH neurons has not been evaluated. Given recent findings linking the ZI with binge-eating behavior,

here we assessed the role of ZI MCH neurons in consumption of palatable food high in fat and sugar (HFHS) in a short-access excessive eating model. To activate ZI MCH neurons, a virus containing an excitatory Designer Receptor Exclusively Activated by Designer Drugs (DREADDs) driven by an MCH promoter was administered selectively to the ZI. Following 7 training sessions where nonrestricted rats had free access to HFHS for 10min in an arena outside of the home cage, the rats reliably consumed ~50% of their 24hr kcal intake during the 10-min HFHS access period. In a post-training test session with 30min HFHS access, results revealed that chemogenetic activation of ZI MCH neurons (via CNO injections) increased consumption of HFHS relative to vehicle (n=18). Next we assessed the role of ZI MCH neurons in normal eating behavior and motivation to work for HFHS in an effort-based choice task. Surprisingly, ICV CNO significantly decreased both 24hr home cage standard chow intake and motivation to work for HFHS (n=14). Consistent with these gain-of-function results, caspase-mediated ablation of ZI MCH neurons reduced HFHS consumption in the short-access excessive eating model and increased 24hr home cage chow intake (n=10 caspase, n=10 sham). Using *in vivo* fiber photometry, we next recorded ZI MCH neuron $Ca^{2+}$ activity during HFHS or chow consumption via a GCaMP6s virus driven by an MCH promoter selectively administered in the ZI. In the short-access excessive eating model, ZI MCH neuron $Ca^{2+}$ activity significantly increased during HFHS eating bouts relative to interbout intervals and this effect was predictive of total calories consumed (n=6). In contrast, during consumption of standard chow following an overnight fast, ZI MCH neuron $Ca^{2+}$ activity significant decreased during chow eating bouts relative to interbout intervals and this effect was also highly predictive of total calories consumed (n=9). Overall, these results show that ZI MCH neurons potentiate consumption of palatable foods, while having opposite effects on intake of consistently accessible bland foods and motivation to work for palatable foods.

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**Poster**

**PSTR038. Ingestion and Energy Balance: Neuropeptides and Hormonal Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR038.10/HH19

**Topic:** F.08. Food and Water Intake and Energy Balance

**Support:** NIH 1R01DK129366-01
Michigan Diabetes Research Center Pilot and Feasibility Award
Whitehall Foundation new investigator grant #2018-08-50

**Title:** Functional interactions between the melanin-concentrating hormone and mesolimbic dopamine systems during food consumption and appetitive learning.

**Authors: *L. E. POTTER**, H. C. LYONS, J. R. EVANS, C. R. BURGESS;
Neurosci., Univ. of Michigan Molec & Behav Neurosci Inst. (MBNI), Ann Arbor, MI

**Abstract:** Hypothalamic melanin-concentrating hormone (MCH)-expressing neurons are thought to promote food consumption and play a role in the integration of internal metabolic signals with appetitive sensory cues. Previous work has pointed to functional interactions between the mesolimbic dopamine (DA) reward system and MCH, and suggested a role for the MCH system in learning. These interactions have not yet been fully characterized *in vivo*. We characterized the rapid dynamics of the MCH and DA systems during consumption of food-rewards, or during food-motivated Pavlovian and instrumental conditioning, by using *in vivo* fiber photometry to monitor GCaMP6s fluorescence in MCH neurons within the lateral hypothalamus, or MCH terminals in the nucleus accumbens (NAc). We also used fiber photometry with dLight1.1 or GRAB-rDA to track changes in DA release within the NAc. Both male and female *pMCH*-cre driver mice were used in these experiments, and no significant sex-differences were observed. We found that both neuron systems are activated during food consumption, and in anticipation of food-rewards (n=6, $p<0.05$ paired student t-tests on group-mean z-scored fluorescence during response vs. baseline phases). Both systems become activated by food-predictive sensory cues after conditioning (n=6, group-mean z-scored fluorescence response to tone vs. baseline $p<0.05$). We further investigated whether the MCH system directly influences DA release in the NAc in these paradigms. After mice were trained and DA/MCH responses stabilized, we suppressed the MCH system's function either by pre-treating with an MCH-receptor 1 (MCHR1) antagonist (SNAP-94847, 10-30mg/kg I.P.), or by chemogenetic inhibition of MCH neurons, while performing simultaneous DA release photometry in the NAc. We found that pre-treatment with the MCHR1 antagonist enhanced DA release in the NAc in response to food rewards (n=5; $p<0.05$ vehicle vs antagonist, paired t-tests on group mean z-scored fluorescence response vs. baseline). We therefore hypothesize that the MCH peptide may tonically suppress DA release in the NAc via MCHR1, a phenomenon which has been suggested previously based on knock-out studies of the *pMCH* or *MCHR1* genes. Preliminary chemogenetic inhibition studies have also demonstrated a trend towards enhanced DA release in the NAc after pre-treatment with the DREADD ligand clozapine-N-oxide (CNO, 3-10mg/kg) in MCH-HM4Di mice, but not HM4Di-negative controls (n=6, two-by-two design). Future experiments will attempt to isolate the effects of glutamatergic signaling by MCH neurons on DA release and NAc function, and make use of optogenetic and pharmacological approaches.

**Disclosures: L.E. Potter:** None. **H.C. Lyons:** None. **J.R. Evans:** None. **C.R. Burgess:** None.

**Poster**

**PSTR038. Ingestion and Energy Balance: Neuropeptides and Hormonal Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR038.11/HH20

**Topic:** F.08. Food and Water Intake and Energy Balance

**Support:** NIDDK # 1F31DK135283-01
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**Title:** Melanin-concentrating hormone neurons differentially regulate feeding and arousal as a function of downstream projection area

**Authors: *K. L. FURMAN**[1,2,3], H. C. LYONS[2,3], J. R. EVANS[2], T. CHA[3,4], L. KIM[2,5], C. R. BURGESS[1,2,3];
[1]Neurosci. Grad. Program, [2]Dept. of Mol. & Integrative Physiol., [3]Michigan Neurosci. Inst., Univ. of Michigan, Ann Arbor, MI; [4]Dept. of Pediatric Otolaryngology, Emory Univ., Atlanta, GA; [5]Lineberger Comprehensive Cancer Ctr., Univ. of North Carolina, Chapel Hill, NC

**Abstract:** Animals must make informed decisions about what and how much to eat in order to maintain energy balance. Yet homeostatic need is not the sole factor in the decision to eat. Non-homeostatic motivators to eat are common, such as craving of sugary or fatty foods even when sated. Dysregulation of such non-homeostatic motivators can contribute to the development of eating disorders. Melanin-concentrating hormone (MCH) neurons of the lateral hypothalamus (LH) and zona incerta are a relevant neural target for both homeostatic and non-homeostatic motivators to eat. MCH neurons project to many brain areas including the arcuate nucleus, nucleus accumbens (NAc), and cerebral cortex, and have a role in numerous behaviors including feeding, sleep, learning, and reward. Injection of MCH peptide into the NAc increases feeding, and chemogenetic activation of MCH neurons that project to the NAc slightly increase food intake in male but not female mice. We hypothesize that MCH projections to the NAc promote hedonic motivations to consume food but do not have a role in sleep-wake regulation. To address this hypothesis, we instrumented MCH-ChR2 mice with EEG/EMG headcaps and optic fibers placed either over the MCH neurons in the LH or their terminals in NAc, and investigated how optogenetic stimulation affected feeding and sleep behavior in different behavioral contexts. When optogenetic stimulation was delivered continuously (473nm, 20Hz, 1s ON 4s OFF for 3hr), we observed that mice with stimulation of MCH neurons in the LH (n = 4) spent more time in REM sleep as well as transitioned into REM sleep bouts more frequently (p < 0.05), while mice with terminal stimulation in the NAc (n= 13) did not show a sleep effect. This continuous stimulation did not significantly increase feeding, regardless of optic fiber location. However, when given the opportunity to choose between a port which delivers both food and acute optogenetic stimulation or a port which delivers stimulation alone, mice with terminal stimulation in the NAc had a significant preference for food paired with stimulation (p < 0.0001), while mice with cell body stimulation of all MCH neurons in the LH did not. Furthermore, these results were consistent between female and male mice. These findings begin to elucidate a mechanism by which MCH neurons differentially regulate feeding and arousal as a function of downstream projection area.

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**Poster**

**PSTR038. Ingestion and Energy Balance: Neuropeptides and Hormonal Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR038.12/HH21

**Topic:** F.08. Food and Water Intake and Energy Balance

**Title:** Control of Feeding by Amygdala PKR2 Neurons

**Authors: *K. R. BOWMAN**, A. MITTAL, T. C. YIN, J. A. SEBAG;
Mol. Physiol. and Biophysics, Univ. of Iowa, Iowa City, IA

**Abstract:** The central nervous system plays a critical role in controlling energy homeostasis. Multiple GPCRs and their ligands modulate neuronal activity to regulate food intake and energy expenditure. Whereas most of our understanding of the central control of feeding focuses on various hypothalamic nuclei, the amygdala is emerging as an important brain region in controlling food intake. In this study, we investigated the role of the Prokineticin Receptor 2 (PKR2) in regulating food intake and body weight. PKR2 is a GPCR coupled to $G\alpha_{q/11}$ and regulated negatively by the Melanocortin Receptor Accessory Protein 2 (MRAP2). PKR2 activation by its agonist PK2 is potently anorexigenic. Interestingly, we found that, while PKR2 is expressed both in hypothalamic and amygdala neurons, the anorexigenic response to PK2 is mediated by amygdala PKR2 neurons. Moreover, our results suggest that PKR2 is especially important for the control of the circadian aspect of food intake since deletion of PKR2 in the amygdala results in increased daytime feeding in mice. Deletion or overexpression of MRAP2 in PKR2 neurons results in increased or decreased anorexigenic activity of PK2 respectively. Overall, this study identifies a new pathway for the circadian control of food intake involving amygdala PKR2 neurons and modulated by MRAP2.

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**Poster**

**PSTR038. Ingestion and Energy Balance: Neuropeptides and Hormonal Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR038.13/HH22

**Topic:** F.08. Food and Water Intake and Energy Balance

**Support:** CONAHCyT CF-2023-I-355

**Title:** Intermittent fasting reduces anxiety-like behavior and reduces mRNA pro-TRH expression in amygdala of adult rats

**Authors: J. TRUJILLO-BARRERA**[1], *P. SOBERANES-CHAVEZ[2], P. DE GORTARI[3];
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**Abstract:** Traditional calorie restriction (CR) is usually employed as a weight loss strategy; however, it also causes stress and anxiety decreasing patients' treatment adherence, which induces their weight regain in 5 years in average. Thyrotropin-releasing hormone (TRH) is a tripeptide that is considered a neuromodulator that among other brain areas is synthesized in amygdala, which is responsible for fear and anxious behavioral responses; in fact, an intracerebroventricular injection of TRH is able to reduce anxiety parameters in the defensive burying behavioral test, and the amygdalar TRH mRNA expression is negatively correlated with rats' anxiety parameters. Intermittent fasting (IF) is used as an alternative feeding regime because limits food consumption to the activity phase of the day and reduces body weight but not generating stress, however, anxiety behavior display has not been evaluated. This study compares anxiety parameters of rats under CR, IF and CR+IF vs. controls. Male Wistar rats kept divided into 4 groups: C=food *ad libitum* all day; CR with all day 30% food restriction of its energy requirements; IF with ad libitum food between 9-17 h; CR+IF with restriction of 30% of its requirements between 9-17 h, (10/group), throughout 4 weeks. IF, CR and CR+IF groups showed 8%, 14%, 25% less weight, respectively than C; IF ate 25% less food than C. At the end of the experiment, rats performed the elevated plus maze test for 5 min, analyzing the latency and number of entries to open (o.a) and closed arms (c.a). The results showed that CR induced more anxiety than C, since the number of entries to o.a was 45% lower accompanied by 2.3 times longer latency; IF and CR+IF had similar number of entries to o.a and lower latency than CR. Thirty minutes after the test, all rats were sacrificed, trunk blood and brain extracted and maintained at -70°C. Serum corticosterone levels in IF were similar to those of C, but CR and CR+IF increased vs C. In amygdalar slices an in situ hybridization histochemical study for TRH expression revealed that in the basolateral nucleus it decreased in all experimental groups, but IF and CR+IF showed it higher than that of CR, supporting that the decreased anxiety of IF group might be associated to a greater amygdalar TRH mRNA expression than in CR. In the present study we concluded that the IF regime does not induce stress or anxiety and that animals with CR+IF did not present the increased anxiety parameters observed in rats only with CR. Therefore, IF seems a better body weight reduction alternative treatment than CR, given that it does not generate anxiety or stress-induced negative emotions.

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**Poster**

**PSTR038. Ingestion and Energy Balance: Neuropeptides and Hormonal Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR038.14/HH23

**Topic:** F.08. Food and Water Intake and Energy Balance

**Support:** NIH Grant DK115762
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**Title:** Regulation of energy balance by the locus coeruleus

**Authors: *S. M. FORTIN**[1], J. C. CHEN[1], M. C. PETTICORD[1,2], G. GODIN[2,3], F. J. RAGOZZINO[3], J. H. PETERS[3], M. R. HAYES[1];
[1]UPenn, Philadelphia, PA; [2]Haverford Col., Haverford, PA; [3]Washington State Univ., Pullman, WA

**Abstract:** Efforts to fully characterize the diversity of mechanisms underlying energy balance control have led to the identification of atypical sites of action for metabolic signals. Here, contribution of the locus coeruleus (LC) to food intake and body weight regulation is described. Using complementary pharmacological, behavioral, electrophysiological, immunohistochemical and genetic approaches in rats, we identify involvement of both LC glucagon-like peptide-1 receptors (GLP-1Rs) and calcitonin receptors (CTRs) to energy balance control. Using microinjections of GLP-1R and CTR agonists to the LC, we show that activation of either LC GLP-1Rs or CTRs potently inhibit food intake and body weight. While aspects of autonomic output related to energy expenditure (i.e. heart rate and body temperature) were affected by either drug manipulation, only LC GLP-1R activation induced kaolin consumption and a suppression of gastric emptying, supporting the hypothesis that LC GLP-1Rs, but not CTRs, contribute to nausea/visceral malaise. In addition to our behavioral data, evidence of pre- and post-synaptic mechanism within the LC for the GLP-1R and CTR, respectively, suggest that that the LC is capable of modulating energy balance through dissociable mechanisms. Additional studies are required to identify the relevant downstream outputs of LC neurons engaged by GLP-1R and CTR signaling and how these circuits interact within the complex network of nuclei that control food intake and body weight regulation.

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**Poster**

**PSTR038. Ingestion and Energy Balance: Neuropeptides and Hormonal Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR038.15/Web Only

**Topic:** F.08. Food and Water Intake and Energy Balance

**Support:** Shanghai Municipal Natural Science Foundation 21ZR1419700
STI 2030—Major Projects 2021ZD0200500

**Title:** Calcitonin Receptor Agonism in the Locus Coeruleus Suppresses Feeding via Aversion

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**Abstract:** Dual amylin and calcitonin receptor agonists (DACRA) are shown to be more effective in reducing body weight than amylin receptor agonists alone. Salmon calcitonin (sCT), a naturally derived DACRA, acts in several brain regions to suppress food intake, promote energy expenditure, and ultimately reduce body weight. However, sCT produces malaise when administered systemically, and the neural mechanism of which remains largely elusive. In the present study, we tested the hypothesis that sCT acts in the locus coeruleus (LC) to induce visceral aversion via enhanced neuronal activity of LC neurons. Intra-LC sCT administration potently suppressed feeding behavior in both fed and fasted mice, and produced conditioned taste aversion. Using slice patch clamp electrophysiology, we tested the effect of sCT on the neuronal activity of the LC. Bath application of sCT enhanced LC pacemaker activity by approximately 30% and this enhancement was blocked by pre-treatment of calcitonin receptor antagonist, AC187. To further investigate the intracellular mechanisms of sCT, we recorded the channel currents of different types before and after bath application of sCT. We found a decrease in L-type calcium currents and medium afterhyperpolarization currents. The latter is associated with the small conductance potassium (SK) channel, which is associated with the LC pacemaker activity. Since intracellular calcium regulates L-type calcium channels, which in turn governs SK channel activity, we investigated the intracellular calcium release mechanism that is responsible for the effect of sCT on the LC. We found that intracellular application of barbadin, BAPTA, or 2-APB, but not PKA, PKC, ERK or JAK/STAT inhibitors, blocked the enhancement effect of sCT on LC pacemaker activity. This indicates that calcitonin receptors in the LC require β-arresting mediated intracellular calcium release to inhibit L-type calcium channels, which associatively reduces SK channel activity, and ultimately increases the pacemaker activity of the LC. Taken together, sCT acts in the LC to produce malaise via enhanced pacemaker activity as a result of reduced SK channel activity. These findings elucidate the key intracellular signaling pathway in the LC neurons that sCT acts on, and provide potential targets for improving the applicability of DACRA in the treatment of obesity.

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**Poster**

**PSTR038. Ingestion and Energy Balance: Neuropeptides and Hormonal Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR038.16/HH24

**Topic:** F.08. Food and Water Intake and Energy Balance

**Support:** Banting and Best Diabetes Centre
CIRTN-R2FRIC CREATE-NSERC

**Title:** Connecting specific central GLP-1 receptors functionally with glucose homeostasis and energy balance

**Authors: *I. SINGH**[1], L. WANG[2], Z. PANG[2,3], D. D. BELSHAM[1,4], M. B. WHEELER[1,5]; [1]Univ. of Toronoto, Toronto, ON, Canada; [2]Rutgers Univ., New Brunswick, NJ; [3]The Child Hlth. Inst. of New Jersey, Robert Wood Johnson Med. Sch., New Brunswick, NJ; [4]Departments of Obstetrics/Gynecology and Med., Univ. of Toronto, Toronto, ON, Canada; [5]Div. of Advanced Diagnostics, Metabolism, Toronto Gen. Res. Inst., Toronto, ON, Canada

**Abstract:** Central nervous system (CNS) control of metabolism plays a pivotal role in maintaining energy and glucose homeostasis. In the brain, Glucagon-like peptide 1 (GLP-1), encoded by the proglucagon '*Gcg' gene*, produced in a distinct population of neurons in the nucleus tractus solitarius (NTS), has been shown to regulate feeding behavior leading to the suppression of appetite. However, neuronal networks that mediate endogenous GLP-1 action in the CNS on feeding and blood glucose are not well understood. This is mainly due to the presence of diverse neuronal subtypes and complex central neuronal connectivity. We systematically analyzed the distribution of GLP-1 receptor (GLP-1R) neurons and axonal projections of $NTS^{Gcg}$ proglucagon expressing neurons in the mouse brain. GLP-1R neurons were found to be broadly distributed in the brain and specific forebrain regions, particularly the hypothalamus, including the arcuate nucleus of the hypothalamus (ARC), received dense $NTS^{Gcg}$ neuronal projections. In addition, we validated the neuronal map of CNS connecting to the pancreas and identified the GLP-1R neurons which might play a role in pancreatic function. We further used this data to study sexual dimorphism in the central innervation of the pancreas. Our result confirmed sex-related difference in the pancreatic innervation. For this reason, the impact of GLP-1 signaling in the ARC, a brain region known to regulate energy homeostasis and feeding behavior was examined. Application of GLP-1R specific agonist Exendin-4 enhanced the ARC pro-opiomelanocortin (POMC) neuronal population's action potential firing frequency and miniature excitatory postsynaptic spontaneous currents amplitude. Using a chemogenetic approach to activate the ARC GLP-1R neurons by using Cre-dependent hM3Dq AAV, we established that activation of the ARC GLP-1R neurons significantly suppressed food intake with an increase in insulin secretion. These results highlight the importance of central GLP-1 signaling within the ARC that express GLP-1R which upon activation, regulates energy homeostasis.

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**Poster**

**PSTR038. Ingestion and Energy Balance: Neuropeptides and Hormonal Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR038.17/HH25

**Topic:** F.08. Food and Water Intake and Energy Balance

**Support:** NIH Grant DK115762

**Title:** Contribution of GLP1 receptor and astrocyte signaling to brainstem glutamatergic neurotransmission in the nucleus of the solitary tract (NTS)

**Authors:** J. E. LINDBERG[1], M. R. HAYES[2], ***J. H. PETERS**[1];
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**Abstract:** The advent of targeting of GLP1 receptors (GLP1R) in the clinical treatment of diabetes and obesity has reignited interest in pharmacotherapies for feeding and metabolic conditions. While the specific receptor system is well characterized pharmacologically, its neuroanatomical distribution is large and the impact of altering its signaling in specific brain areas remains an open set of questions. A key area in the control of feeding and metabolism is the brainstem nucleus of the solitary tract (NTS). The NTS receives direct viscerosensory afferent information via the vagus to convey the status of the gastrointestinal tract and integrates this information with endocrine and local signals. The NTS is well known to control feeding, including the processes of satiety, and both the NTS and vagal afferent neurons are reported to contain GLP1R expressing cells, including astrocytes. While selective agonists and antagonists exist for GLP1Rs, determining the contribution of astrocyte to changes in neurotransmission is much more challenging. This set of studies aims to determine the cellular effects of GLP1R activation of glutamatergic neurotransmission and determine the extent to which astrocytes contribute to these effects. We utilized patch-clamp electrophysiology and fluorescent calcium imaging in the ex vivo brainstem slices and cultured primary afferent neurons to delineate the contributions of GLP1R and astrocytes in brainstem glutamatergic signaling in the NTS. We found GLP1R activation with exendin 4 (Ex-4) increased the frequency of spontaneous glutamate release in a subpopulation of NTS neurons. This effect was reversed following pretreatment with the competitive GLP1R antagonist exendin 9-39 (Ex 9-39). Preliminary data in isolated vagal afferent neurons demonstrated Ex-4 can directly increase cytosolic calcium in a subpopulation of afferents, suggesting GLP1R may be mediating increased glutamate release via the central vagal terminals in the NTS. In parallel, metabolic disruption of NTS astrocytes with fluorocitrate strongly suppresses glutamate release, while astrocyte activation with PAR-1 agonism increase glutamate release. The effects of GLP1R on glutamate signaling may be mediated via astrocyte to neuronal signaling, as reported previously using complementary approaches, and will be determined directly using astrocyte selective pharmacology on Ex-4 signaling. Together our data support the ability of GLP1Rs to control glutamate signaling in the NTS, possibly via presynaptic vagal terminal activation or perhaps via recruitment of astrocyte signaling.

**Disclosures: J.E. Lindberg:** None. **M.R. Hayes:** None. **J.H. Peters:** None.

**Poster**

**PSTR038. Ingestion and Energy Balance: Neuropeptides and Hormonal Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR038.18/HH26

**Topic:** F.08. Food and Water Intake and Energy Balance

**Title:** Preemptive satiation modulation by glp1 pathway in mouse and human

**Authors: *H. SHIN**, K. KIM, J. PARK, K. KIM, Y. LEE, S. JUNG, M. PARK, H. CHOI; Biomed. Sci., Seoul Natl. Univ., 103, Daehak-ro, Jongno-gu, Seoul, Korea, Republic of

**Abstract:** Eating behavior is regulated by integrating information from the external environment and internal body state for efficient survival. It is paramount for the brain to compute real-time information and send feed-forward signals to our body to drive feeding behavior. In this context, it is legitimate to say that our body needs to prepare the termination of eating behavior beforehand to avoid over-feeding through preemptive satiation. However, the mechanism of preemptive satiation and where in our brain this phenomenon takes place remains unclarified. In our research, activation and inhibition of DMH GLP-1R neurons significantly and immediately increased and decreased eating behavior, respectively. Further, in natural eating behaviors , DMH GLP-1R neurons are significantly activated upon food availability before the initiation of eating behavior. Whereas these neurons are deactivated when eating is terminated. These results imply that DMH GLP-1R neurons encode preemptive satiation. Using miniscope (nVoke) during eating behaviors, single-cell neural activities of DMH GLP-1R neurons are monitored to distinguish which neurons are activated at food availability or food consumption time points. In addition, micro-endoscope distinguished a subpopulation of DMH GLP1R neurons that respond to GLP-1 injection. Furthermore, a clinical trial comprised of phase-specific food sensory delivery and corresponding questionnaires is performed to study the effects of GLP-1 administration on preemptive satiation in humans. Collectively, our research demonstrate that DMH GLP-1R neurons regulate preemptive satiation. This study can give a new perspective on the mechanism of anti-obesity drugs and the development of future obesity treatment.

**Disclosures: H. Shin:** None. **K. Kim:** None. **J. Park:** None. **K. Kim:** None. **Y. Lee:** None. **S. Jung:** None. **M. Park:** None. **H. Choi:** None.

**Poster**

**PSTR038. Ingestion and Energy Balance: Neuropeptides and Hormonal Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR038.19/HH27

**Topic:** F.08. Food and Water Intake and Energy Balance

**Support:** NIH grant R01DK095757

**Title:** Bed nucleus of the stria terminalis GLP-1R neuron effects on feeding behavior

**Authors: I. I. COIDURAS**[1], L. R. ANDERSON[1], S. TRAPP[2], F. REIMANN[3], F. M. GRIBBLE[3], *D. L. WILLIAMS[1];
[1]Psychology, Florida State Univ., Tallahassee, FL; [2]Neuroscience,Physiology & Pharmacol., Univ. Col. London, London, United Kingdom; [3]Univ. of Cambridge, Cambridge, United Kingdom

**Abstract:** Activation of glucagon-like peptide 1 receptors (GLP-1R) in the bed nucleus of the stria terminalis (BNST) suppresses food intake. To investigate the mechanisms for this effect, we examined feeding effects of chemogenetic activation of BNST GLP1R neurons. Male and female GLP-1R-Cre mice received intra-BNST injection of AAV to induce hM3Dq-mCherry (n = 6M, 6F) or control mCherry (n = 5M, 5F) in GLP-1R neurons. Mice were housed in the BioDAQ continuous food intake monitoring system for measurement of intake and meal pattern variables. They received IP injection of either vehicle or CNO (1 mg/kg) 20 min before dark onset, in counterbalanced order separated by 48 h. Chow intake was significantly suppressed by CNO for the first 6 hours of dark in mice that expressed hM3Dq in GLP-1R neurons (23-44% reduction, p's<0.05), along with first meal size (53% reduction, p<0.05), but there were no effects in control mice, and no sex differences were observed. We previously showed that GLP-1R stimulation directly inhibits 60% of GLP-1R-expressing BNST neurons, and that some BNST GLP-1R neurons project to the lateral hypothalamus (LH). Because the BNST GLP-1R neuron population is heterogeneous, we hypothesized that those that project to LH affect food intake differently than those that project elsewhere. To test this, GLP-1R-Cre mice were injected with AAVs as described above, and bilateral cannulas were implanted in the LH for chemogenetic activation of GLP-1R neuron terminals. Intra-LH vehicle (VEH) or CNO injections were made 30 min before dark onset in counterbalanced order separated by at least 48 h. CNO had no effect on chow intake in hM3Dq mice (n=7M, 7F) or controls (n=4M, 4F). We then asked if CNO could attenuate the effect of 15-min restraint stress prior to dark onset, because we have previously reported that BNST GLP-1Rs have a role in stress-induced hypophagia. However, stress suppressed intake similarly in both groups regardless of CNO treatment. Next, we examined effects on high-fat diet (HFD, 60% fat) intake. Mice were maintained on HFD for 4 weeks and then received intra-LH VEH or CNO. hM3Dq mice (n=7M, 9F) significantly increased cumulative HFD intake after CNO by 25-45% at multiple timepoints (p's<0.05), with no effect in controls (n=6M, 8F), and no sex differences were observed. Meal size tended to increase after CNO in hM3Dq mice, but we saw no significant effect on meal pattern variables. We conclude that the GLP-1R BNST-to-LH neuron projection influences food intake under some circumstances, and the anorexic effects of BNST GLP-1R neuron activation are mediated by neurons that project elsewhere.

**Disclosures: I.I. Coiduras:** None. **L.R. Anderson:** None. **S. Trapp:** None. **F. Reimann:** None. **F.M. Gribble:** None. **D.L. Williams:** None.

**Poster**

**PSTR038. Ingestion and Energy Balance: Neuropeptides and Hormonal Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR038.20/HH28

**Topic:** F.08. Food and Water Intake and Energy Balance

**Support:** NIH NIDDK P30DK098722
Joseph and Vera Long Foundation
NIH NIDDK P30 DK63720

**Title:** Identification of AgRP cells in the murine hindbrain that drive feeding

**Authors: *T. P. BACHOR**[1], K. ATTAL[1], F. MIFSUD[1], V. PHAM[1], E. VAGENA[1], R. HUARCAYA[1], M. VALDEARCOS[1], K. W. WILLIAMS[2], C. VAISSE[1], A. W. XU[1];
[1]Diabetes Ctr., Univ. of California San Francisco, San Francisco, CA; [2]Intrnl. Med., Univ. Texas Southwestern, DALLAS, TX

**Abstract:** The central melanocortin system is essential for the regulation of food intake and body weight in both humans and rodents. Agouti-related protein (AgRP) is the sole orexigenic component of the central melanocortin system and is conserved across mammalian species. AgRP is currently known to be expressed exclusively in the mediobasal hypothalamus, and hypothalamic AgRP-expressing neurons are essential for feeding. Here we describe a previously unknown population of AgRP cells in the area postrema (AP) and the adjacent subpostrema area (SubP) and commissural nucleus of the solitary tract (cNTS) of the mouse hindbrain (termed $AgRP^{Hind}$ herein). $AgRP^{Hind}$ cells consisted of locally projecting neurons as well as tanycyte-like cells, and hindbrain AgRP expression was low under *ad libitum* fed condition but increased upon food deprivation. In adult mice that lacked hypothalamic AgRP neurons, chemogenetic activation of AgRP neurons resulted in hyperphagia and weight gain. In addition, transcranial focal photo-stimulation of AgRP cells above the AP area with a step-function opsin with ultra-high light sensitivity (SOUL) stimulated feeding in mice with or without hypothalamic AgRP neurons, suggesting that the hyperphagic effects of $AgRP^{Hind}$ neurons are independent of hypothalamic AgRP neurons. Thus, our findings delineate the existence and function of a previously unknown population of AgRP cells in the mouse hindbrain that drives feeding. This study may pave the way for future anti-obesity therapeutic interventions targeting AgRP neurons in the area postrema, an area outside the blood-brain barrier that enables easy access of therapeutic agents.

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**Poster**

**PSTR038. Ingestion and Energy Balance: Neuropeptides and Hormonal Control**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR038.21/II1

**Topic:** F.08. Food and Water Intake and Energy Balance

**Support:** F31HD106890
NIH R01DK106476
NIH T32DK007563

**Title:** Developmental programming of convergent signals impacting feeding and drinking

**Authors: *S. R. SWEET**[1], G. L. YU[1], J. B. ZIMMERMANN[1], J. E. BIDDINGER[2], R. B. SIMERLY[2];
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**Abstract:** Dehydration is a common occurrence in response to water scarcity caused by drought, limited access to clean water, or disease. Drinking and feeding are coordinated homeostatic events, illustrated by the phenomenon of dehydration-anorexia, but our understanding of the development of converging hypothalamic neural circuits that link drinking and feeding remains rudimentary. Moreover, many environmental factors influence formation of neural circuits during the early postnatal period, leading to long-term physiological changes. Agouti-related peptide (AgRP) neurons originating in the arcuate nucleus of the hypothalamus (ARH) are substrates of developmental programming, responding to nutritional cues during a postnatal critical period of development to reach downstream targets. The paraventricular nucleus of the hypothalamus (PVH) receives inputs from both the ARH and the median preoptic nucleus (MePO) to regulate energy and fluid homeostasis, respectively, representing a possible node of integration. To determine the age at which MePO projections reach the PVH, we used Fos-labeling in response to dehydration in wild-type neonatal mice and used DiI axonal labeling to visualize development of projections. Our results indicate neurons in the MePO respond to a hypertonic saline (HS) stimulus by the end of the first week of life while densities of Fos-labeled nuclei in the PVH do not peak until the second postnatal week, preceding innervation of the PVH by AgRP neurons. Based on these observations, we hypothesized hyperstimulation of MePO neurons in neonatal mice may impact the formation of AgRP circuitry with sustained changes in energy balance. To test this hypothesis, neonatal mice were exposed to HS treatment daily from postnatal day (P) 5 to P15 and immunohistochemistry was used to evaluate the density of AgRP innervation in the MePO and PVH at P60. Adult male mice that received HS treatment from P5-P15 ($HS^{PN}$) displayed significantly increased densities of AgRP axons in the PVH, while female mice displayed a significant decrease in the MePO. When exposed to a high fat diet, food intake in adult male $HS^{PN}$ mice was greater than in control mice. Observed perturbations in food intake suggest dehydration-anorexia may also be impacted by $HS^{PN}$ treatment. We are testing this notion experimentally, and using TRAP2 mice and whole-brain imaging to identify subpopulations of neurons where drinking and feeding signals converge. Together, these results suggest development of feeding circuits is impacted by postnatal hyperactivation of neural circuits regulating drinking, with lasting consequences for energy balance regulation.

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**Poster**

**PSTR039. Fear Generalization and Threat Avoidance**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR039.01/II2

**Topic:** G.01. Fear and Aversive Learning and Memory

**Support:** JTF Grant 61911
Sponsored by a grant from the Supporting Structures: Innovative Partnerships to Enhance Bench Science at CCCU Member Institutions

**Title:** Automated classification of behavior across mouse and rat strains during foraging and simulated aerial 3D owl attack

**Authors: H. K. ABOUEICH**[1], M. E. MAINS[1], B. A. WELLS[1], S. A. GOLDEN[3], *P. M. BAKER[2,1];
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**Abstract:** Recent interest has grown in utilizing ethologically relevant stimuli in the laboratory setting to characterize important behaviors such as fear learning or risk-based foraging. One approach has been to utilize simulated aerial predator attacks in rodents such as a simulated 3D owl during open field foraging. Comparing these with other forms of aerial threat such as projected looming stimuli could reveal the range of responses to specific threat that animals may experience and underlying differences in neural processing. However, due to the relatively unrestricted behavior of animals in such tasks, connecting the wide range of behaviors available to subjects to moment-to-moment neural activity can be difficult. To address this, the current study utilized pose estimation from Deep Lab Cut combined with further analysis of behaviors using the package Simple Behavioral Analysis (SimBA), to characterize a range of behaviors in response to a simulated aerial attack from a 3D printed owl in a repeatable fashion. The behavior took place in a large foraging arena in which subjects are habituated to foraging for food and returning to a closed end of the arena that serves as a safe hide for 5 minutes a day. After eight days of habituation, a 3D printed owl (40cm wing span) was introduced above the far end of the arena, attached to a swing arm controlled by Arduino software. For the subsequent two days, each time the subject came within ~20 cm of the food, the owl surged down and forward into the arena in a simulated attack. The behaviors of mice (CFW, CD1, C57/B6) and rats (Sprague-Dawley) was examined and included group vs individual housing conditions and sex, in order to understand the conditions under which strong or weak fear responses might be elicited in this paradigm. Subjects demonstrated a range of behaviors both within and between groups including fleeing an attack event, freezing, or spending increased time in the safe zone of the arena even before the initial attack event. Results revealed that generally, rats exhibit a stronger fleeing response following an attack event than mice. Additionally, foraging behavior in mice varies depending on individual vs. group housed conditions as well as inbred vs. outbred strains. Across all groups, the presence of the owl reduced the amount of time spent in the arena when the owl was present (45.4s ±10.2) compared to the last three days of habituation (130.7s ± 7.5). Taken together, these results point to a need to consider the extraneous conditions and strain used when considering a response to predator threats under controlled conditions and a range of behavior needs to be measured to capture both individual and group variability.

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**Poster**

**PSTR039. Fear Generalization and Threat Avoidance**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR039.02/II3

**Topic:** G.01. Fear and Aversive Learning and Memory

**Title:** Contribution of CRF- and SOM-expressing BNST neurons in early cued fear learning

**Authors: *V. ZLOTNIK**[1], K. LYONS[1], L. HALLADAY[2];
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**Abstract:** Understanding the mechanisms underlying our responses to threats and other stressors is crucial since they contribute to our susceptibility to developing trauma-related disorders. Specifically, we focus on the role of the bed nucleus of stria terminalis (BNST) that has been implicated in aspects of anxiety and threat processing. While our field has characterized some of the neural signaling in the BNST that promotes fear and threat responses, the specific role of the BNST in associative fear learning is still unclear and yet to be investigated. Prior research in our lab identified two sub-populations of BNST cells that exhibited distinct neural firing patterns during cued fear learning. “Ramping” BNST cells’ firing rates corresponded with learning; their activity was positively correlated with fear expression, suggesting that ramping cells may encode long-term information about stimuli predicting danger. “Phasic” BNST cells were most active during the initial stages of forming the association between the cue and aversive outcome. Phasic cells were active when mice did not express much freezing behavior, suggesting that they may encode more ambiguous threats, and may be important for decision-making in the face of uncertain stimuli. In addition, other studies have shown that two types of cells in the BNST are activated during fear memory consolidation. These include corticotropin-releasing factor-expressing (CRF) and somatostatin-expressing (SOM) neurons. Our current work takes advantage of transgenic mice and cell-specific chemogenetics to understand how CRF- and SOM-expressing cells in the BNST contribute to early cued fear learning.

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**Poster**

**PSTR039. Fear Generalization and Threat Avoidance**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR039.03/II4

**Topic:** G.01. Fear and Aversive Learning and Memory

**Support:** NIMH IRP 1ZIAMH002950

**Title:** A thalamostriatal circuit that shapes dopamine-mediated safety signaling during avoidance learning

**Authors:** J. MA[1], ***E. E. MACDONALD**[2], M. A. PENZO[3];
[1]Natl. Inst. Of Mental Health, Natl. Inst., Natl. Inst. Of Mental Health, Natl. Inst., Bethesda, MD; [2]NIMH, Bethesda, MD; [3]Natl. Inst. of Mental Hlth., Natl. Inst. of Mental Hlth., Bethesda, MD

**Abstract:** Active avoidance (AA) is an adaptive defensive strategy employed to minimize threat encounters. However, excessive avoidance is a core feature of anxiety disorders in humans, thus highlighting the necessity of understanding the neural mechanisms that underlie avoidance behaviors. A key brain region involved in the expression of avoidance is the nucleus accumbens (NAc), located within the ventral striatum. Inactivation of the NAc diminishes avoidance, and dopamine (DA) release within this region is classically associated with both the learning and execution of avoidance behavior. For instance, DA release immediately after successful avoidance responses (termed 'safety period') is thought to mediate avoidance learning via positive reinforcement. Still, the mechanisms that shape this process remain unknown. Here, we discovered that NAc-projecting neurons of the paraventricular nucleus of the thalamus (PVT) - a structure that is critical for the expression and maintenance of AA behavior - are selectively engaged during the safety period of the AA task. Importantly, optogenetic inhibition of the PVT-NAc pathway during the safety period diminished avoidance learning. These data suggested that safety related DA signaling in NAc and modulation of PVT input during these episodes might be related. In agreement, we found that activation of PVT terminals can promote DA release in NAc and that silencing the PVT-NAc pathway impairs safety-related DA. Additional evidence collected from us point at local modulation of cholinergic interneurons as a plausible mechanism by which the PVT shapes DA release in NAc. Overall, our results provide novel evidence of a thamostriatal pathway that is critical for the learning of active avoidance likely by promoting the reinforcing actions of DA release during the safety period.

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**Poster**

**PSTR039. Fear Generalization and Threat Avoidance**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR039.04/II5

**Topic:** G.01. Fear and Aversive Learning and Memory

**Support:** NIH Grant 5R01NS094550
NIH Grant 3P20GM121310-04S2
NIH Grant P20GM121310

**Title:** Learning induced perceptual switch in the primary somatosensory cortex

**Authors: *J. DAI**[1], Q.-Q. SUN[2];
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**Abstract: Learning induced perceptual switch in the primary somatosensory cortex**
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Affiliations:Department of Zoology and Physiology, University of Wyoming, Laramie, WY82071, USA.Wyoming Sensory Biology Center of Biomedical Research Excellence, University of Wyoming, Laramie, WY82071, USA.
**Abstract**
Increasing evidence suggests that during learning, multi-dimensional inputs are integrated within the sensory cortices. However, the strategies by which the sensory cortex employs to achieve learning remain poorly understood. We studied the neural cording of trace eyeblink conditioning (TEC) learning in head-fixed freely running mice, where whisker deflection was used as a conditioned stimulus (CS) followed by an air puff to the cornea (unconditioned stimulus, US) after an interval. A set of behavior changes, including maintaining the closure of eyelids, and decreased reverse running between CS and US onset, are hallmark features of animal who learned the task. The local blockade of S1 activities with muscimol abolished the behavior learning suggesting that S1 is required for the TEC. In naive animals, based on the response properties to the CS and US, responsive primary neurons (PNs) were divided into two subtypes: CR neurons (i.e. CS-responsive neurons) and UR neurons (i.e. US-responsive neurons). After animals learned the task, CR neurons become less responsive to CS, while UR neurons gain responsiveness to CS, a phenomenon we coined as 'learning induced perceptual switch (LIPS)'. To explore the potential mechanisms underlying LIPS, we found that systemic and local (i.e. in S1) administration of the nicotinic receptor antagonist during TEC training blocked the LIPS, and concomitantly disrupted the behavior learning. Additionally, we monitored responses of three types of cortical interneurons (INs) and observed that the responses of the somatostatin-expressing (SST), but not parvalbumin-expressing (PV) INs' are negatively correlated with the learning performance, suggesting that SST-INs contribute to the LIPs. Thus, we conclude that L2/3 PNs in S1 encode discriminability efficiently by LIPS like mechanisms, and cholinergic pathways and cortical interneurons are involved in the formation of LIPS.

**Disclosures: J. Dai:** None. **Q. Sun:** None.

**Poster**

**PSTR039. Fear Generalization and Threat Avoidance**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR039.05/II6

**Topic:** G.01. Fear and Aversive Learning and Memory

**Title:** Continuous and partial reinforcement impact threat expectancies in conceptual fear generalization

**Authors: *S. MITRA**, M. K. ASTHANA;
Indian Inst. of Technol. Roorkee, Roorkee, India

**Abstract:** Background: Fear generalization involves eliciting conditioned fear responses to novel stimuli which share perceptually or conceptually similar properties with the conditioned stimulus (CS). Overgeneralization of fear plays a significant role in the acquisition and maintenance of anxiety disorders. However, fear generalization is also adaptive since it may prevent individuals from experiencing the same negative outcome by avoiding situations that predict negative consequences. The reinforcement levels of the unconditioned stimulus (UCS) impact fear acquisition and generalization. The current study explored the effect of UCS reinforcement (i.e., continuous and partial) on the threat expectancies in conceptual fear generalization due to category-based similarity using a visual aversive UCS. Methods: Fear generalization can be studied using the category-based conditioning paradigm, where individuals are conditioned to members of a specific category rather than a single stimulus. Further, the generalization of conditioned responses is tested with novel exemplars from the same category with which prior conditioning has not occurred. The CSs were exemplars from four categories, i.e., animals, insects, appliances, and mechanical tools. The UCS was an aversive image (No. 3051) with negative valence and high arousal, selected from International Affective Picture System (IAPS) database. A required sample size of 15 was determined using G*power analysis with an alpha value of 0.05, power of 0.95, and a predetermined medium effect size of 0.40 using one-way repeated measures ANOVA. Twenty-two healthy participants 18 to 21 years (M=19.18, SD= 0.17) underwent fear acquisition with exemplars from the four stimulus categories, with varying UCS reinforcement levels (0%, 37.5%, 62.5%, and 100%). Subsequently, fear generalization was tested with novel unreinforced exemplars from each category. Online UCS expectancy ratings were obtained using a 9-point Likert scale in each experimental phase.Results: Repeated measures ANOVA reflected a significant effect of reinforcement on the UCS expectancy and CS-UCS contingency ratings. UCS expectancy ratings increased with increasing reinforcement levels in the generalization phase [$F(1.593, 33.454) = 59.423$, $p < 0.001$, $\eta_p^2 = 0.739$]. Conclusions: The current study suggests that partial and continuous UCS reinforcement levels directly impact conceptual fear generalization. Our study shows that individuals tend to overgeneralize fear when the threat is unpredictable. Furthermore, our findings demonstrate how fear generalizes using less aversive stimuli (visual) as the UCS.

**Disclosures: S. Mitra:** None. **M.K. Asthana:** None.

**Poster**

**PSTR039. Fear Generalization and Threat Avoidance**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR039.06/II7

**Topic:** G.01. Fear and Aversive Learning and Memory

**Support:** NIH Grant R25GM060566.

**Title:** Effect of Predator Odor on Conditioned and Unconditioned Defensive Behaviors in Syrian Hamsters

**Authors:** *C. MARKHAM[1], **D. FLETCHER**[1], P. PARKER[1], R. NORRIS[2], A. CHILDS[1];
[1]Psychology, [2]Biol., Morehouse Col., Atlanta, GA

**Abstract:** Biologically relevant odors, including those related to predators, will induce fear and anxiety-like behaviors, including risk assessment, avoidance and freezing in laboratory animals. In addition, animals previously exposed to predator odors will show conditioned place avoidance. In contrast, animals exposed to non-biological, but aversive odors, such as formaldehyde, will also exhibit defensive behaviors, but importantly, they do not show conditioned place avoidance. While there are many studies examining the effect of predator odors on defensive responding in rats and mice, there is currently a dearth of information using hamsters as test subjects. In this study, biological and non-biological odors were used to evaluate both unconditioned and conditioned defensive responses in male Syrian hamsters. Specifically, we examined whether coyote predator odors will elicit unconditioned avoidance behaviors in hamsters using a novel runway box. We compare these effects to formaldehyde, a non-biological odor. We found that while subjects exposed predator odors elicited a significantly higher level of defensive behaviors and avoidance compared to both the control and formaldehyde group, no significant differences were observed on the conditioned responses. These results not only add to the existing literature regarding the neurobiological basis of innate avoidance behavior, it also demonstrates key species differences in defensive behaviors in response to predator odors.

**Disclosures: C. Markham:** None. **D. Fletcher:** None. **P. Parker:** None. **R. Norris:** None. **A. Childs:** None.

**Poster**

**PSTR039. Fear Generalization and Threat Avoidance**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR039.07/II8

**Topic:** G.01. Fear and Aversive Learning and Memory

**Title:** Contextual generalization to tactile and visual cues in male and female C57BL/6J mice

**Authors:** N. I. BELLE, **I. L. DWYER**, M. ZAYOUR, *A. ZUNIGA;
Col. of Wooster, Wooster, OH

**Abstract:** Post-traumatic stress disorder (PTSD) is a debilitating disorder often characterized by intrusive thoughts and flashbacks that are connected to the traumatic event previously experienced. Often, PTSD patients will experience symptoms even when in a safe setting. This phenomenon, referred to as generalization, is believed to occur with time, and reflects the possibility that fearful and traumatic memories become less context-specific as time passes.

Previous research has shown that similarities between contexts, testing order, and sex all influence contextual generalization. Of note however, these previous findings have produced mixed results, potentially due to procedural variations between studies. Here, we sought to expand our understanding of contextual generalization by examining the role of tactile and visual cues within a context in male and female mice. Male and female C57BL/6J mice were exposed to a 3-shock contextual fear conditioning protocol. Following fear conditioning, mice were separated into a 24-hour or 15-day group, and were tested either 24hrs after training, or 15 days later. On test day, mice were tested in either context A (the original context) or context B (a novel context with alternate flooring and walls). Freezing behavior during the test was recorded and scored manually, and brains were harvested and processed for c-Fos immunohistochemistry. Results showed a main effect of both Time and Context on the levels of freezing, as well as a Time X Context interaction, indicating generalization. We found no main effect of Sex, nor any Sex-based interactions, indicating that males and females did not differ in either freezing or generalization. Immunohistochemistry for c-Fos, a marker of neuronal activity, found that there was increased activation of the ventral hippocampus in the 15-day group. Indeed, we only observed a significant main effect of time for c-Fos expression in the ventral hippocampus. Our results provide further evidence that contextual generalization can arise over time, and that sex may not affect this under certain parameters. Lastly, our results show that the ventral hippocampus may be involved in contextual generalization. Future studies are needed in which we investigate more remote time points, different contextual feature changes, as well as activation patterns of areas beyond the ventral hippocampus.

**Disclosures:** **N.I. Belle:** None. **I.L. Dwyer:** None. **M. Zayour:** None. **A. Zuniga:** None.

**Poster**

**PSTR039. Fear Generalization and Threat Avoidance**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR039.08/II9

**Topic:** G.01. Fear and Aversive Learning and Memory

**Support:** Australian Research Council Discovery Project DP200102969

**Title:** Second-order conditioning involves formation of competing excitatory and inhibitory associations.

**Authors: *D. P. H. COHEN**, J. P. FAM, V. LAURENT, R. F. WESTBROOK, N. M. HOLMES;
Sch. of Psychology, Univ. of New South Wales, Sydney, Australia

**Abstract:** Humans and animals are constantly presented with conflicting information. However, little is known regarding how contradictory information is processed in the brain, particularly when the conflict originates as part of the same event. One way this can be studied is through second-order fear conditioning. A standard protocol consists of three stages. In stage 1, rats are

exposed to pairings of an initially innocuous stimulus, S1 (e.g., a tone), with an innately aversive unconditioned stimulus (US, e.g., foot shock; first-order conditioning of S1). In stage 2, rats are exposed to pairings of another initially innocuous stimulus, S2 (e.g., a light), with the already-conditioned S1 (second-order conditioning of S2). Finally, in stage 3, rats exhibit fear (freezing) when tested with presentations of S2 alone. A distinct feature of this protocol is that while S2 is paired with the learned source of danger S1, it also comes to be correlated with the absence of the US i.e., while S2 is present the US never occurs. We hypothesized that during S2-S1 pairings, S2 encodes two conflicting associations: specifically, S2 signals the learned source of danger, S1 (S2-danger) whilst simultaneously signaling safety as the US never occurs when it is present (S2-safety). The present study tested this hypothesis by exploiting the fact that safety associations are often encoded in a specific region of the medial prefrontal cortex: the infralimbic cortex (IL). Specifically, using female and male Long-Evans rats, we examined whether silencing neuronal activity in the IL (via infusions of the GABA agonist, muscimol) would enhance second-order conditioning by preventing encoding/expression of the S2-safety association. The results showed that silencing the IL during S2-S1 pairings in stage 2 or presentations of S2 in stage 3 resulted in enhanced freezing to S2; and this was conditional on the absence of the US in stage 2. These findings are taken to support our hypothesis that two contradictory associations are encoded concurrently during second-order conditioning and that these associations stand in competition with each other.

**Disclosures: D.P.H. Cohen:** None. **J.P. Fam:** None. **V. Laurent:** None. **R.F. Westbrook:** None. **N.M. Holmes:** None.

**Poster**

**PSTR039. Fear Generalization and Threat Avoidance**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR039.09/II10

**Topic:** G.01. Fear and Aversive Learning and Memory

**Support:** NIMH Grant R15 MH127534-01

**Title:** Infralimbic neuronal ensemble dynamics underlying fear memory generalization over time

**Authors: *R. SUBRAMANIAN**, K. DRAKE, O. CARPENTER, A. BAUMAN, S. ROZENTAL, C. CHO, D. PETERSON, D. S. CHAVEZ, H. THOMPSON, A. JENKINS, S. EHNSTROM, T. TSUKUDA, H. KOOLPE, H. C. BERGSTROM;
Vassar Col., Poughkeepsie, NY

**Abstract:** Novel encounters with stimuli that signal the potential for threat necessitate the generalization of defensive responding. One factor that contributes to the degree of generalization is the passage of time. A brain region that has been consistently linked with modulation of fear memory expression is the medial prefrontal cortex (mPFC). How mPFC synaptic plasticity over time is associated with changes in fear memory generalization is

unknown. To test this question, ArcCreER$^{T2}$ x eYFP transgenic mice were leveraged to visualize "neuronal ensembles" in the prelimbic (PL) and infralimbic (IL) subregions of the mPFC. In these experiments, all mice were fear conditioned using a 5-kHz auditory CS. Later, at recent (7 day) or remote (30 day) timepoints, mice were presented with either the CS again, a novel "ambiguous" 3-kHz tone, or no tone (context control). Measurements of co-activated cell populations at the recent time point revealed a greater number of co-activated cells in L2/3 IL were associated with the "ambiguous" stimulus. At the remote time point, fewer L2/3 IL reactivated cells were associated with the ambiguous tone. While generalization did increase modestly over time, throughout these experiments we observed high variability in freezing to the ambiguous cue. A cluster analysis of freezing responses revealed no differences in the number of reactivated cells between mice that exhibited "high generalization" or "low generalization" at either recent or remote timepoints. Next, we silenced the IL using chemogenetics during the presentation of the ambiguous stimulus. IL inactivation promoted generalization, supporting a role for the IL in reducing fear to ambiguous, but potentially threatening, stimuli. Overall, these data identify plasticity of IL ensembles that are formed, and perhaps, suppressed over time in response to an ambivalent threatening stimulus. These data also indicate that IL activity may not necessarily linearly scale with the freezing response, but rather, may signal to downstream structures the presence of a novel stimulus with ambivalent threatening properties. Finally, these data support a role for the IL in modulating fear responses in the presence of an ambiguous stimuli.

**Disclosures: R. Subramanian:** None. **K. Drake:** None. **O. Carpenter:** None. **A. Bauman:** None. **S. Rozental:** None. **C. Cho:** None. **D. Peterson:** None. **D.S. Chavez:** None. **H. Thompson:** None. **A. Jenkins:** None. **S. Ehnstrom:** None. **T. Tsukuda:** None. **H. Koolpe:** None. **H.C. Bergstrom:** None.

**Poster**

**PSTR039. Fear Generalization and Threat Avoidance**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR039.10/II11

**Topic:** G.01. Fear and Aversive Learning and Memory

**Support:** NIMH R15 MH127534-01

**Title:** Inter-individual differences in fear generalization predict extinction performance

**Authors: T. TSUKUDA**, A. BAUMAN, R. SUBRAMANIAN, *H. C. BERGSTROM; Psychological Sci., Vassar Col., Poughkeepsie, NY

**Abstract:** In the natural environment, rarely do environmental stimuli occur in the same place or take the same form. An essential mechanism that allows for the transfer of learned experience to other stimuli and contexts is known as stimulus generalization. While the ability to generalize stimuli is adaptive, *over*generalization of stimuli is maladaptive, and has been linked with

clinical disorders such as anxiety and post-traumatic stress disorder (PTSD). Various associative learning components, including fear conditioning, generalization, and extinction, are used for studying maladaptive behaviors and circuits likely dysregulated in PTSD. A well-recognized feature of both fear generalization and extinction is high variability. It has been proposed that preclinical models of trauma-related disorders should include the study of individual differences. In this series of experiments, we screened a large cohort of ArcCreER$^{T2}$ X eYFP mice (C57BL/6J background) on anxiety tests (elevated zero maze and the novel open field) and cued fear generalization and extinction tests. Results revealed a wide spectrum of cued fear generalization. Subsequent cluster analysis producing "high generalization" and "low generalization" phenotypes uncovered a relationship between generalization performance and extinction performance in males; the greater the generalization, the greater the extinction deficit. In females, there was no relationship between generalization and extinction. Rather, generalization performance was correlated with anxiety-related behavior; the greater the generalization, the greater the anxiety-like behavior. Interestingly, neither fear conditioning nor extinction performance were predictors of anxiety, making generalization a unique predictor of both extinction performance and anxiety. These data shed new light on a sex-dependent relationship between fear generalization performance and both unconditioned and conditioned fear. These data underscore the importance of considering both inter-individual and sex differences in fear conditioning for the preclinical study of trauma- and stressor-related disorders such as PTSD.

**Disclosures: T. Tsukuda:** None. **A. Bauman:** None. **R. Subramanian:** None. **H.C. Bergstrom:** None.

**Poster**

**PSTR039. Fear Generalization and Threat Avoidance**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR039.11/II12

**Topic:** G.04. Emotion

**Support:** ISF-NSFC joint research program (grant No. 3459/20)
BSF grant No. 2019186

**Title:** Distinct neural activity in the social brain network of SD rats during affiliative and aversive social interactions

**Authors: *S. R. JOHN**, S. NETSER, S. WAGNER;
Sagol Dept. of Neurobio., Univ. of Haifa, Haifa, Israel

**Abstract:** This study aims to investigate the neural mechanisms underlying social behavior in SD rats. Social behavior is a natural phenomenon that is essential for survival across the animal kingdom. An environmental stimulus can elicit a repertoire of behavioral responses, and the animal will decide whether to approach or avoid the stimulus based on the positive or negative

valence of the stimulus. Despite the importance of social behavior, many fundamental questions remain unanswered in our understanding of brain circuits and the underlying neural mechanisms of social behavior.Our main working hypothesis is that coordinated neuronal activity across the social brain reflects differential behavioral responses of social approach or avoidance. To test this hypothesis, we implanted custom-made multielectrode array probes in the brains of adult male SD rats and recorded electrophysiological activity from multiple brain regions simultaneously while the rats performed the Social Preference task using novel social stimuli. We analyzed both multiunit spiking activity and local field potential signals recorded from various brain regions, including the amygdaloid complex, a central hub for driving emotional behaviors.The results showed that changes in power of LFP frequencies were dependent on the valence of the social stimulus, as reflected by the rat's behavior towards the social stimulus. Approach or avoidance behaviors were differentially correlated with significant changes in power of Theta and Gamma oscillations in specific areas of the amygdaloid complex, including the medial, central, stria terminalis, and anterior amygdala. In contrast, MUA in the social brain regions did not show significant changes except in the brain areas of AA and STIA during appetitive and aversive states. Additionally, Theta and Gamma oscillations showed differential coherence patterns between social brain regions during affiliative and aversive social encounters. We also observed changes in vocalization, with rats producing more ultrasonic calls 50kHz when prosocial and long 22kHz calls when stressed.This study provides insight into the neural mechanisms underlying socio-emotional internal states of SD rats during both affiliative and aversive social behaviors. The findings suggest that specific oscillatory activities in the amygdala complex are involved in the estimation and processing of social stimuli and the expression of adaptive behavioral responses. These results could be beneficial in understanding changes in brain activity involved in brain pathologies associated with atypical social behavior, potentially leading to improved therapeutic interventions.

**Disclosures:** **S.R. John:** None. **S. Netser:** None. **S. Wagner:** None.

**Poster**

**PSTR040. Neuronal Circuits, Motivation, and Emotion**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR040.01/II13

**Topic:** G.03. Motivation

**Support:** NIH-R01-MH120136
Rising STARs Award from the University of Texas System
Brain & Behavior Research Foundation Grant (NARSAD Young Investigator

**Title:** Distinct subpopulations of prelimbic cortex neurons encode the salience or the motivational value of reward-cues during approach-avoidance conflict test in rats

**Authors: *V. CHUONG**, G. AQUINO-MIRANDA, X. ZHANG, F. H. DO MONTE;
Dept. of Neurobio. & Neuroanatomy, Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX

**Abstract:** To survive in nature, animals need to identify environmental cues associated with reward or threat and make adaptive responses. Neurons in the prelimbic (PL) subregion of the medial prefrontal cortex change their firing rates in response to reward- and threat-associated cues and play an essential role in encoding contextual information. The PL contains two non-overlapping subpopulations of neurons that project to either the paraventricular nucleus of the thalamus (PVT) or the nucleus accumbens (NAc), both regions involved in action-selection and risky decision-making. However, it remains unclear how these two subsets of PL neurons respond during situations of conflict when reward and threat cues occur together. To explore this question, male adult Long-Evans rats previously trained to press a lever for sucrose during the presentation of audiovisual cues were implanted with single-unit recording electrodes in the PL. Rats were then exposed to an approach-food vs. avoid-predator odor conflict model comprised of three phases: (i) reward phase, only food cues presented, (ii) cat odor phase, only a fear-inducing cat odor presented, and (iii) conflict phase, food cues concomitantly presented with cat odor. The next day, rats were returned to the same chamber and exposed to the food cues in the absence of the predator odor (fear-inducing context). Rats displayed increased defensive behaviors and reduced food seeking during the conflict phase compared to the reward phase. Tracking the activity of the same cells across the phases revealed that most PL neurons (230 out of 413 neurons, 29 rats) changed their firing rates in more than one phase, and ~70% of these cells responded in opposite directions, suggesting valence encoding. Using a combination of single-unit recordings and optogenetics to photoidentify PL neurons based on their projection target, we found that PL-PVT neurons responded to food cues with a similar magnitude in both reward and conflict phases. In contrast, PL-NAc neurons that were excited or inhibited during the food cues in the reward phase responded in the opposite direction in the conflict phase. Consistently, during fear-inducing context exposure, a subset of PL-NAc neurons that were excited during the food cues when rats failed to press the lever (i.e., risk-avoiding trials) did not respond when they pressed (i.e., risk-taking trials). Together, our results suggest that PL-PVT neurons encode information about the salience of the food cues during both reward and conflict phases, whereas PL-NAc neurons encode changes in the motivational value of the food cues from reward to conflict phases according to the behavioral choice of the animals.

**Disclosures: V. Chuong:** None. **G. Aquino-Miranda:** None. **X. Zhang:** None. **F.H. Do Monte:** None.

**Poster**

**PSTR040. Neuronal Circuits, Motivation, and Emotion**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR040.02/II14

**Topic:** G.03. Motivation

**Support:** NIH R01-MH120136
Brain & Behavior Research Foundation Grant
Rising STARs Award

**Title:** Prelimbic cortex neurons discriminate between ultrasonic vocalizations of different valences in rats

**Authors: *N. ELINSON-WATSON**, F. H. DO MONTE, G. AQUINO-MIRANDA;
Univ. of Texas Hlth. Sci. Center, Houston, Houston, TX

**Abstract:** Adult rats emit distinct types of ultrasonic vocalizations (USVs) that reflect the valence of their emotional states. 22 KHz USVs are emitted during negative emotional states (aversive), whereas 50 KHz USVs occur mostly during positive emotional states (appetitive). However, there is still some debate on whether the emission of aversive vs. appetitive USVs by an emitter rat can bidirectionally regulate the behavioral responses of a receiver rat. Also unclear is which brain regions encode both types of USVs. One candidate region is the prelimbic subregion of the prefrontal cortex (PL), a structure implicated in the regulation of social behaviors and decision-making processes. Male adult Long-Evans rats with single-unit recording electrodes implanted in PL were exposed to pre-recorded aversive and appetitive USV playbacks during the same session. A 22 KHz artificial sound was used as a control stimulus. An analysis of 375 neurons recorded from 20 rats revealed two subpopulations of PL cells that responded to either aversive USVs (14.4%, 7.4% excited and 7% inhibited) or appetitive USVs (11.8%, 4.6% excited and 7.2% inhibited), indicating that PL neurons can discriminate between appetitive and aversive vocalizations. Interestingly, ~65% of PL neurons that changed their firing rates in response to 22 KHz USVs did not respond to 22 KHz artificial sound, suggesting that distinct populations of cells in PL encode USV calls vs. sounds of the same frequency. Next, to check whether aversive and appetitive USV playbacks affect animal's behavior, rats previously trained to press a lever for sucrose during the presentation of a light cue were exposed to the USV playbacks (22 KHz or 50 KHz) or the artificial 22 KHz sound either 10 s before or during the 10 s of the sucrose cue presentations. We found that aversive or appetitive USV playbacks before or during the sucrose cues did not change sucrose-seeking. To test if live emission of aversive USVs is required to affect reward seeking in the receiver rat, a separate subset of animals was used. *Demonstrators* were given electrical foot shocks in a chamber while *observers* were pressing for sucrose in an adjacent chamber separated by a grid. Interestingly, *observers* exposed to *demonstrators* that emitted aversive USVs during the foot shock session had lower sucrose seeking and higher freezing responses compared to either baseline or *demonstrators* that didn't emit aversive USVs. Together, our results establish a role for PL neurons in the discrimination of USVs of different emotional valences, and reveals that the communicative function of aversive USVs requires a richer social context to elicit behavioral changes in the receiver animals.

**Disclosures: N. Elinson-Watson:** None. **F.H. Do Monte:** None. **G. Aquino-Miranda:** None.

**Poster**

**PSTR040. Neuronal Circuits, Motivation, and Emotion**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR040.03/II15

**Topic:** G.03. Motivation

**Support:** 1R21MH131363-01
2P20GM121310

**Title:** A prefrontal motor circuit drives motivated movement

**Authors: *Y. WANG**[1], Q.-Q. SUN[2];
[1]Univ. of Wyoming, Laramie, WY; [2]UNIVERSITY OF WYOMING, Univ. of Wyoming, laramie, WY

**Abstract:** Motivation and sensation signals arise from deep brain regions, such as amygdala, insular cortex, and hypothalamus. However, it is unclear how these signals affect the voluntary movements. Here, using ChR2-assisted circuit mapping, we identify a group of medial prefrontal cortex (mPFC) motor cortex projecting (MP) neurons linking the deep brain regions (amygdala and insular cortex) with the somatic motor regions (primary motor cortex and striatum). Applying single-unit extracellular recordings and opto-tagging approach in awake mice, we find that MP neurons encode movement phases, but not valence and motor command in a persistent licking task. Optogenetically inactivation of MP neurons impairs the initiation of persistent licking movement. Interestingly, cross-correlation of spike data reveals that the licking signal is not triggered by the valence signal. A computational model suggests that a short but continuous sensory stimulus activate MP neurons mediating the initiation of movement. Together, our results reveal a brain mechanism that transforms sensation inputs to voluntary movement outputs.

**Disclosures: Y. Wang:** A. Employment/Salary (full or part-time); University of Wyoming. **Q. Sun:** A. Employment/Salary (full or part-time); University of Wyoming.

**Poster**

**PSTR040. Neuronal Circuits, Motivation, and Emotion**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR040.04/II16

**Topic:** G.03. Motivation

**Title:** Orbitofrontal and infralimbic neuronal processing of adaptive versus maladaptive avoidant responses in a novel operant safety task.

**Authors: *D. GABRIEL**[1], S. SANGHA[2];
[1]Indiana Univ. Sch. of Medicine; Stark Neurosciences Res. Inst., Indianapolis, IN; [2]Dept. of Psychiatry, Indiana Univ. Sch. of Med., Indianapolis, IN

**Abstract:** Active avoidance is an evolutionarily beneficial behavior wherein aversive events may be prevented through proactive, threat mitigating behaviors. However, continued patterns of

avoidant behavior in the absence of any threat, or in the presence of safety signals, are maladaptive. The orbitofrontal (OFC) and infralimbic (IL) cortices are critical regions for processing and integrating motivational information to guide adaptive responses. Furthermore, dysregulated OFC and IL functional activity is commonly associated with maladaptive patterns of avoidant behavior and inefficient use of safety signals. Understanding how these regions guide and regulate active avoidance may give critical insight to the etiology of disorders associated with perseverative avoidant behavior.Here, we created a novel mixed operant/Pavlovian safety learning task in which male and female Long Evans rats learn to press a lever to prevent a mild footshock signaled by an auditory fear cue. This active avoidance response ends the fear cue and activates a visual safety signal indicating successful avoidance. In a subset of "safety" trials, the safety cue is presented either alone or concurrently with the fear cue. These trials are always shock free, making avoidant responses unnecessary. Once trained, electrode arrays are surgically implanted in OFC and IL within the same hemisphere (counterbalanced across subjects) to record single unit activity during 2 behavioral probe sessions. In these probes, rats are presented for the first time with a choice of 2 levers during a safety shock-free trial: one that has been associated with liquid sucrose, and another that has been associated with shock avoidance. Thus, avoidant lever presses reduce rewarding outcomes, indicating a maladaptive bias toward perseverative avoidant behavior. In the second probe, both reward and avoidance levers are also presented during active avoidance trials. Unlike safety trials, avoidant responses in these trials are still necessary to obtain optimal outcomes. Thus, this assesses rats' ability to maintain distinct goal-oriented behaviors, i.e. avoid punishers and pursue rewards. This novel mixed operant/Pavlovian safety task offers the opportunity to assess the behavioral development and neuronal underpinnings of maladaptive avoidant behaviors common in clinical disorders that can be resistant to treatment.

**Disclosures:** **D. Gabriel:** None. **S. Sangha:** None.

**Poster**

**PSTR040. Neuronal Circuits, Motivation, and Emotion**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR040.05/II17

**Topic:** G.03. Motivation

**Support:** National Institute of Mental Health Intramural Research Program (ZIA MH002970-04)
Brain and Behavior Research Foundation NARSAD Young Investigator Award to HAT
NIH Center for Compulsive Behavior Fellowships to RFG
NIH Post-Doctoral Research Associate Training Fellowship to RFG

**Title:** Investigating the role of the ventromedial prefrontal cortex in approach-avoidance conflict in mice

**Authors: *R. FLORES GARCIA**, M. AWANYAI, M. ARENIVAR, H. WANG, B. AVERBECK, H. A. TEJEDA;
Natl. Inst. of Mental Hlth., Bethesda, MD

**Abstract:** Approach-avoidance conflict arises when individuals are confronted with stimuli or situations involving both rewarding and aversive contingencies. Psychiatric disorders, including depression and addiction, often manifest with maladaptive conflict resolution strategies. Therefore, it is important to understand the neural mechanisms underlying decision-making during approach-avoidance conflict. In this study, we performed single-cell *in-vivo* calcium imaging in the ventromedial prefrontal cortex (vmPFC), a key area of the brain involved in threat suppression and executive control, of mice while training in an approach-avoidance conflict task. Over six days, mice were first trained to nose poke for sucrose rewards, with nose pokes reinforced by an Ensure reward during a 30-second light cue. Subsequently, mice underwent ten days of conflict training in the platform-mediated avoidance task. Conflict was introduced by presenting a 30-second tone cue that co-terminated with a foot shock. In order to avoid getting shocked, mice had to forgo reward seeking and step onto a plexiglass platform on the corner opposite of the reward port before the end of the tone cue. The tone had complete, partial, or no overlap with the reward cue, generating high, medium, or minimal conflict trials, respectively. We employed a neural encoding model to identify the behavioral and task variables encoded in the vmPFC. Our findings revealed that the proportion of neurons encoding nose-poking behavior and light cue stimulus increased across training days, consistent with the behavioral findings that mice displayed increased nose-poking behavior during the cue. During the approach-avoidance conflict phase, we observed neurons in the vmPFC encoding various stimuli, including the light, tone, co-presentation cue, shock, and nose-poking behavior. Ongoing analyses are underway to determine whether there are distinct neural representations in the vmPFC for active versus passive behaviors and whether these shift dynamically throughout training. These findings provide valuable insights into the neural circuits and encoding patterns that underlie the modulation of approach and avoidance strategies during motivational conflict.

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**Poster**

**PSTR040. Neuronal Circuits, Motivation, and Emotion**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR040.06/II18

**Topic:** G.03. Motivation

**Support:** Army Research Office W911NF-16-1-0474
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**Title:** Orbitofrontal and anterior cingulate circuits in primates: complementary roles in cost-benefit decision-making and learning

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**Abstract:** Mood-related disorders prevalence and diagnosis have increased over the last few decades. Although we have an improved understanding of the underlying pathophysiology, we still lack a thorough understanding of brain structures and circuitries that could underlie these. For this purpose, we attempted to investigate two cortical regions, key components of a critical corticostriatal circuitry: the pregenual anterior cingulate cortex (pACC) and the caudal orbitofrontal cortex (cOFC) in non-human primates. The pACC previously has been linked to learning, decision-making and mood regulation. However, the cOFC, a posterior part of the orbitofrontal cortex (OFC), has received limited scientific attention; most research on the OFC has focused on more medial or lateral parts of this cortical region. In order to achieve a better understanding of this circuitry, we trained two adult macaque monkeys (one male, one female) on a visually guided approach-avoidance (Ap-Av) task. A similar version of this task has been previously used in both non-human primate and human research. During the task, monkeys, previously implanted with standard chronic platinum iridium probes or acute S-probes, had to choose either to accept or reject offers indicating conjoint, specific amounts of reward and punishment. In addition to electrophysiological recordings and task performance measurements, physiological measures, including pupil diameter, lick rates and pulsimetry, were recorded to estimate the behavioral state of the animals. After both animals mastered the task, and exhibited stable behavior throughout, and during separate days, electrical microstimulation (EMS) was delivered. Analysis of the electrophysiological data during learning showed that units in both pACC and cOFC are responsive to most task events, with pACC being more active than the cOFC during the cue offer onset period, and cOFC more active during the outcome period, especially during the delivery of negative outcome (i.e., airpuff). EMS during a number of sessions, and in specific small sites within either region, induced increased avoidance behavior, i.e., avoiding most offers. These results demonstrate a complimentary role of pACC and cOFC in cost-benefit decision-making processes, while at the same time demonstrating their causal relationship to mood regulation.

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**Poster**

**PSTR040. Neuronal Circuits, Motivation, and Emotion**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR040.07/II19

**Topic:** G.03. Motivation

**Support:** NIH Grant NIDA 044980
NARSAD Young Investigator

**Title:** Phasic signals in the rat prelimbic cortex and nucleus accumbens core in a stressor controllability task predict future resilience to fear and motivational shifts

**Authors:** K. T. SILETTI-BROWN, K. A. SILETTI-BROWN, J. B. TORRES, ***M. P. SADDORIS**;
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**Abstract:** While stress is a virtually unavoidable aspect of life, how individuals respond to similar situations can vary quite significantly. For some, the experience of a potent stressor will elicit transient negative emotional states followed by rapid recovery to normal affect, while for others, this experience can lead to persistent traumatic states such as post-traumatic stress disorder (PTSD), anxiety or depression. One of these individual risk factors depends on whether individuals perceive that they can exert control over a stressful situation (i.e., actions can alter or mitigate aversive outcomes) versus situations under which they have no control, a phenomenon termed “learned helplessness”. This well-established approach in rats has demonstrated those with behavioral control typically show resilience to future stressors, while those lacking control show susceptibility to other stressors. This difference appears to depend on signals from the prefrontal cortex, where manipulations such as pharmacology or lesions abolish the ability for rats to benefit from a behaviorally controllable experience. However, to date, there has been no recording of neural activity prefrontal cortex or related limbic targets to characterize the computations necessary for learning about controllable versus uncontrollable stressors. In this study, we recorded single-unit activity in the prelimbic (PL) prefrontal cortex and the nucleus accumbens core (NAc) in male and female rats who were assigned to one of three groups in a cued variant of a stressor controllability task: (1) Escapable Shock (ES), where rats could rotate a wheel to terminate an unavoidable tail shock, (2) Inescapable Shock (IS), where rats received shocks onset/offset yoked to an ES rat, but could not rotate the wheel, and (3) homecage controls (HC), who received the shock-associated cue alone without aversive consequences. To assess the trans-situational effects of ES/IS on both reward and aversion, these rats were then run on a Pavlovian reward task (3d), followed by fear conditioning task. Neural firing in both PL and NAc showed greater phasic activity for ES stimuli (cue/shock) than either IS or HC. In the subsequent Pavlovian reward task, ES rats showed greater phasic activity in NAc (but not PL) to reward-predictive cues over repeated experience with the task compared to IS rats. In the fear conditioning task, male and female IS rats showed significantly greater fear than either ES or HC rats to both cues and context. Overall, these data suggest that differential phasic activity during ES/IS can predict individual susceptibility to later motivational and aversive experiences.

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**Poster**

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**Topic:** G.03. Motivation

**Support:** NIH Grant 1ZIAEY000415

**Title:** Inactivation of Periaqueductal Gray Neurons Impairs Primate Oculomotor Engagement in Goal-Directed Behaviors

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**Abstract:** Higher levels of motivation are likely to increase an individual's behavioral control, making them more confident in their ability to carry out the behavior. This, in turn, increases the likelihood that they will engage in goal-directed behavior. The present study aimed to investigate the role of periaqueductal gray neurons in signaling reward outcomes and their impact on primate engagement and performance in goal-directed behaviors. Our results revealed that periaqueductal gray neurons were strongly excited in the context of low reward expectations. We observed a correlation between this neuronal activation and an increase in saccadic eye movements toward the outside of the target area, subsequently decreasing the monkey's engagement in the task. Conversely, periaqueductal gray neurons were tonically suppressed in the context of high reward expectations, which correlated with an increase in holding gaze inside the target area. This, in turn, suppressed unnecessary eye movements and increased the monkey's engagement in the task and performance of subsequent goal-directed behaviors. Additionally, we conducted experiments involving the injection of the GABA agonist muscimol into the periaqueductal gray, which induced a deceleration of eye movements and remarkable relaxation in the monkeys. Intriguingly, this induced severe relaxation and suppression of even necessary task performance behaviors and led to drowsiness. Overall, our study provides compelling evidence for the participation of the periaqueductal gray in signaling reward expectations and its impact on primate oculomotor engagement and performance in goal-directed actions. The periaqueductal gray exhibits extensive connectivity with various brain regions involved in reward expectation, eye movement control, and motivational behaviors. Notably, these connections encompass the lateral habenula, superior colliculus, and oculomotor nuclei, suggesting that the involvement of the periaqueductal gray extends beyond the regulation of eye movements and modulation of the oculomotor system during motivational behaviors. Further research in this area holds promise for deepening our understanding of the complex interplay among motivation, emotion, and eye movement control, with potential implications for diverse clinical investigations.

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**Poster**

**PSTR040. Neuronal Circuits, Motivation, and Emotion**

**Location:** WCC Halls A-C

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**Topic:** G.03. Motivation

**Support:** Consejo Nacional de Ciencia y Tecnología (CONACyT grant INFR-281265)

**Title:** Strain differences in performance of a progressive ratio schedule in C57 and CD1 mice during development

**Authors: *J. BURITICÁ**[1], T. CAMPOS-ORDOÑEZ[2];
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**Abstract:** Reinforcement schedules analyze reward-seeking behavior, voluntary drug intake or drug self-administration to identify the maladaptive behaviors and drug target in animal models. Progressive ratio (PR) schedule of reinforcement is a method of quantitative estimation of motivation which an animal will make to obtain a reward. Inbred C57BL/6J and outbred ICR (CD1) mice showed differences in locomotion, cognitive flexibility, or aggression. However, these strains have not been compared on a PR schedule of reinforcement to analyze motivation during early adolescence. Male and female C57BL/6J and CD1 mice were evaluated by open field to analyze locomotion at P21. We used a PR3 schedule for ten consecutive days (P30-P40). PR3 performance was evaluated by the breakpoint, and the mathematical principles of reinforcement (MPR) was used to dissect motivation, impulsivity, and motor skills to manipulate the operandum in mice (P30-P40). CD1 mice showed a higher locomotor activity than C57BL/6J independently of sex, $p < 0.001$. CD1 mice had a higher breakpoint, however, male CD1 mice produce a gradual increase of breakpoint until the last session, $p < 0.001$. In MPR model, CD1 mice showed a decrease in fixed paused (impulsivity) than C57BL/6J independently by sex, $p = 0.001$. Therefore, our data suggest that the origin of the higher breakpoint in CD1 strain may related to the impulsivity. MPR model can be useful to analyze the origin of breakpoint dissecting factors such as motivation, impulsivity, and motor skill during a PR in adolescents CD1 and C57BL/6J mice. These findings are important to stablish the behavioral phenotypes between CD1 and C57BL/6J mice and the potential predisposition to use them in several animal models of substance-use and misuse.

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**Poster**

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NARSAD Young Investigator Award by the Brain and Behavior Research Foundation, to S.B.

**Title:** Dissociable encoding of motivated behavior by parallel thalamo-striatal projections

**Authors: C. LAMPERT**[1], A. TELLEZ[1], B. MACHEN[3], I. KHAN[4], C. GAO[5], E. MCDONNALD[6], M. A. PENZO[5], *S. BEAS[2];
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**Abstract:** The successful pursuit of goals requires effectively carrying out and ending actions that lead to positive outcomes. This process relies on internal motivational states driven by factors like hunger or fear. However, we still lack a complete understanding of how the brain monitors and influences motivational states to shape goal-oriented actions. The paraventricular nucleus of the thalamus (PVT), located in the midline thalamus, plays a role in guiding motivated behaviors via its projections to the nucleus accumbens (NAc) and has been shown to monitor internal states through interoceptive inputs from the hypothalamus and brainstem. Recent research has identified two distinct subpopulations of PVT neurons: Type1PVT and Type2PVT. These subpopulations differ in their genetic characteristics, functionality, and connections with other brain regions, including the NAc. In this study, we utilized fiber photometry to investigate the real-time dynamics of these two PVT neuron types in mice engaged in a reward foraging task. Our findings revealed that Type1PVT neurons encode the execution of goal-oriented actions, while Type2PVT neurons are involved in signaling the termination of such actions. Additionally, Type1PVT neuronal activity was correlated with motivational parameters like vigor and satiety, whereas Type2PVT cells did not show such correlations. Remarkably, these characteristics remained largely intact even when focusing on the activity of PVT projections specifically targeting the NAc. Altogether, our study demonstrates the presence of two distinct thalamo-striatal projections through which the brain dynamically regulates the pursuit of goals. It sheds light on the mechanisms by which the brain tracks motivational states to shape purposeful actions.

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**Poster**

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**Location:** WCC Halls A-C

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**Topic:** G.03. Motivation

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**Title:** The role of extended amygdala CRF in incentive motivation and addiction

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

**Abstract:** Corticotropin releasing factor (CRF) neurons are traditionally assumed to generate aversive stress states (George et al., 2012). However, other evidence shows that CRF neurons in nucleus accumbens (NAc) and central amygdala (CeA) can generate positively-valenced incentive motivation to pursue and consume rewards (Lemos et al., 2012; Peciña et al., 2006). For example, optogenetic laser stimulation of CRF neurons in the CeA and NAc of crh-Cre rats intensifies and focuses pursuit of a laser-paired sucrose or cocaine reward over an equal reward without laser stimulation, and also supports laser self-stimulation of CRF neurons indicating positive valence of CRF neuronal excitation in CeA and NAc (Baumgartner et al., 2021, 2022). However, several major issues remain. First, CRF neurons co-release other neurotransmitters. Thus, it is unknown whether CRF itself versus other neurotransmitters mediate the positively-valenced motivation. To specifically test the role of CRF peptide, we administered i.c.v. microinjections of a nonspecific CRF antagonist or of vehicle prior to CeA or NAc laser self-stimulation by crh-Cre rats, or prior to 2-choice tasks in which rats could choose to earn either laser-paired sucrose reward or identical sucrose reward without laser. Preliminary results suggest that CRF receptor blockade reduces incentive motivation effects from optogenetic stimulation of CRF neurons in CeA and NAc, indicating a positively-valenced role for CRF neurotransmitter. We are now exploring the relative roles of CRF projections from the CeA to the lateral hypothalamus, dorsal medial striatum, and ventral tegmental area. A second major issue remaining is that the motivational valence effects of CRF in extended amygdala have been posited to become more negative after chronic drug exposure, growing as an aversive b-process to produce withdrawal, distress, and relapse in addiction (Koob, 2010). A potential CRF switch in motivational valence from positive to negative is consistent with reports that severe stress experiences reverse the motivational valence of CRF signaling in NAc (Lemos et al., 2012). To test whether CRF neuronal activation in CeA or NAc similarly switches valence from positive to negative after extensive drug consumption, we give crh-Cre rats 2 weeks exposure to daily 6-hour long access cocaine self-administration. We then assess the motivational valence of optogenetic CRF neuronal stimulation in CeA using laser self-stimulation, laser avoidance, and sucrose two-choice tasks. This work helps clarify the multiple roles for CRF neurons in CeA and NAc in driving motivation that could contribute to addictive relapse and drug seeking.

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**Poster**

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**Topic:** G.03. Motivation

**Support:** R01 Grant MH130331

**Title:** Signaling of salience and prediction errors by the anterior insula

**Authors: *L. F. GOMEZ-ALATORRE**[1,2], A. AMIR[1], A. KARKI[1], M. HERZALLAH[1], D. PARE[1];
[1]Ctr. for Mol. and Behavioral Neurosci. (CMBN), Rutgers University-Newark, Newark, NJ;
[2]Behavioral and Neural Sci., Rutgers Univeristy-Newark, Newark, NJ

**Abstract:** In fMRI studies, the anterior insula (AI) is recruited in a wide variety of tasks, indicating that it fulfills a core function needed in many contexts. In keeping with this, fMRI and LFP recording studies in humans suggest that the AI encodes the salience of stimuli and deviations from expectations, signals that can mobilize cognitive resources and facilitate learning. However, BOLD signals and LFPs do not have sufficient resolution to assess how these codes are distributed across AI cells. Here, we addressed this question using multi-site single unit and LFP recordings in Long Evans rats performing a novel reinforcement learning task. In this task, hungry rats are presented with tones associated with different reward amounts (CSs) and noxious stimuli. Rats are trained to nose-poke at one end of the arena, triggering the presentation of one of three tones (CS1; 60 db; 0.7 s) that signal how many food pellets can be retrieved at the other end (0, 1, or 3 food pellets for tones of 0.5, 4, or 8 kHz tone). Rats then run to the arena's midpoint where they must nose-poke a second time, triggering a second tone (CS2), which is either the same (80% of trials) or a different tone (15% of trials) than CS1, confirming or challenging their reward expectations, respectively. Most AI neurons (78%) showed significant task-related activity (signed-rank tests $p<0.01$): 56% changed their firing rates in response to one or more of the CSs, 47% in anticipation of reward delivery, and 23% in response to the noxious sound. Of the CS responsive cells, 29% had no response or an inhibition to CS1 and increased their firing rate to CS2, 41% showed the opposite, 24% were excited by both, and 5% were inhibited by both. To assess salience encoding by AI neurons, we examined whether they responded to both the noxious and reward-predicting tones. We found extensive overlap: 94% of cells excited by the noxious sound were also excited by one or more of the appetitive CSs; 39% of cells excited by appetitive CSs were also responsive to the noxious noise. Thus, a large proportion of AI neurons encode salience. To assess AI encoding of prediction errors (PE), we compared their responses to the same CS2 when it was preceded by the same (congruent) or a different CS1 (incongruent). 54% of AI cells showed a congruency effect (response to congruent CS2 < response to same incongruent CS2), whether the incongruent CS2 signaled an increase or decrease in reward, consistent with an unsigned PE signal. Overall, our results indicate that AI cells concurrently respond to several variables, shedding light on the role of the AI in signaling salience and deviations from expectations, both core cognitive functions required in many contexts.

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**Poster**

**PSTR040. Neuronal Circuits, Motivation, and Emotion**

**Location:** WCC Halls A-C

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**Topic:** G.03. Motivation

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**Title:** Selective silencing of the ventral striatum-ventral pallidum pathway enhances approach choices and motivational states under approach-avoidance conflict in nonhuman primates

**Authors: *J. N. OH**[1], S. AMEMORI[1,2], K.-I. INOUE[3], K. KIMURA[3], M. TAKADA[3], K.-I. AMEMORI[1];
[1]Inst. for the Advanced Study of Human Biol. (ASHBi), Kyoto Univ., Kyoto, Japan; [2]Japan Society for the Promotion of Sci. (JSPS), Tokyo, Japan; [3]Ctr. for the Evolutionary Origins of Human Behavior, Kyoto Univ., Inuyama, Japan

**Abstract:** Motivation in decision-making varies depending on the conflict types. When faced with two desirable job offers (i.e., an approach-approach (Ap-Ap) conflict), we can make decisions with high motivation. On the other hand, when we need to decide whether to accept or reject a job providing a high salary but entailing a heavy workload (i.e., an approach-avoidance (Ap-Av) conflict), the decision-making can be challenging, leading to reduced motivation. However, the neural system underlying motivation in conflict conditions remains unknown. The pathway from the ventral striatum (VS) to the ventral pallidum (VP) has been implicated in both seeking rewards and avoiding aversive situations. We thus hypothesized that the VS-VP pathway plays a causal role in regulating motivation, particularly in the context of Ap-Av conflict. To address this, we trained two macaque monkeys to perform two tasks: the Ap-Ap task in which they had to choose between rewarding options, and the Ap-Av task in which they had to decide whether to accept or reject an offer of paired reward and aversive air-puff (each ranging from 0 to 100%). To manipulate the VS-VP pathway, we introduced the inhibitory hM4Di receptor gene into VS neurons using a viral vector (AAV2.1-CaMKII-hM4Di) and locally infused deschloroclozapine (DCZ) to the VP to suppress input from the VS. We observed a significant elevation in the monkeys' motivation in the Ap-Av task after DCZ infusion. The pathway manipulation significantly reduced the frequency of omission error (t-test, $P < 0.05$) and the

reaction time for the target selection (t-test, $P < 0.01$), as compared to the control condition. We further observed the increase in the Ap choice (t-test, $P < 0.05$) and obtained the sharpened tuning curve (t-test, $P < 0.01$), especially when the offered air-puff was strong (i.e., > 75%). Importantly, the DCZ infusion did not change the motivational state in the Ap-Ap task (t-test, $P > 0.05$). To characterize the functional role of the VP, we recorded the cue-period activity from 173 neurons therein and found predominant activities correlated with either positive value (n=41 out of 51 value-coding activities) or motivation (n=27 out of 45 motivation-coding activities). In line with the characteristics of VP neurons, we found that manipulating the VS-VP pathway increased both motivation and valuation in decision-making. Our findings suggest that disinhibiting VP neurons may potentially result in increased motivation and positive valuation, particularly under the Ap-Av conflict. The present results support the idea that the VS-VP pathway is crucial in regulating motivation, especially in situations involving aversive contexts.

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**Poster**

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**Topic:** G.03. Motivation

**Support:** National Institute on Alcohol Abuse and Alcoholism Intramural Research Program Grant No. ZIA-AA000401
Postdoctoral Research Associate Training fellowship from the Center on Compulsive Behaviors

**Title:** Amygdalar regulation of punished decision-making.

**Authors: *P. PIANTADOSI**, S. PERRY, R. SANDON VELIZ, K. CODEN, H. CHOI, N. SPITZ, N. SCHWAB, M. AUTHEMENT, V. ALVAREZ, A. HOLMES, J. SCHAFFER, D. DA SILVA;
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**Abstract:** Cost/benefit analyses are disturbed in substance use disorders and have been suggested to be mediated by interactions between cortico-limbic-striatal circuits. Within these circuits, the basolateral amygdala (BLA) has been shown to be critical for aversive costs like punishment to produce flexible changes in actions. Yet, it remains unclear how the BLA facilitates such flexibility. Here, we used *in vivo* 1-photon imaging, fiber photometry, and optogenetic manipulation in male mice to detail BLA function during cost/benefit decision making, identifying a BLA to nucleus accumbens shell (NAcSh) projection that contributes to action flexibility. Mice were first trained to discriminate between one reward port that delivered a large amount of milkshake reinforcement, and another that delivered a small amount. Mice

then received risky decision-making task (RDT) sessions whereby selection of the large reward was associated with a minor footshock that ascended in likelihood across three trial blocks (0, 50, and 75% probability). Selection of the small reward option was never punished. Throughout training and RDT sessions, GCaMP6-based fluorescence was imaged using microendoscopic 1-photon imaging. During reward magnitude training, subsets of BLA neurons displayed consistent responses to rewarded events during the pre-choice and post-choice period, while others developed or lost responsivity over multiple days of training. The introduction of punishment risk during the RDT dramatically affected behavior: mice deliberated longer prior to making a choice, displayed behaviors characteristic of anxiety-related indecision, and gradually shifted their choice towards the small, safe reward. This shift was associated with changes in BLA neuron activity: for example, many neurons encoded footshock punishment, with most being recruited from a pool of cells that were not reward-excited. We next assessed whether signaling in a discrete BLA-NAcSh pathway was sensitive to risk and causally related to flexibility. Using projection-specific fiber photometry and 1-photon imaging, we observed that the BLA-NAcSh population was less sensitive to footshock punishment than the overall BLA population, but pathway activity preceding actions was significantly inhibited by punishment risk. To test whether this inhibition causally contributed to actions, we optogenetically excited BLA terminals in the NAcSh, which produced a robust increase in risk-seeking. These data provide novel insight into the manner in which BLA processes punishing information, with ongoing experiments exploring further differences in projection-specificity and transcriptional profile.

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**Poster**

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**Program #/Poster #:** PSTR040.15/II27

**Topic:** G.03. Motivation

**Support:** Center on Compulsive Behaviors Fellowship

**Title:** Paradoxical Responses of Medial Septal GAD2 Neurons to Reward and Punishment: Potential role during stress-induced coping

**Authors: *C. CALVA**[1], J. COUDRIET[2], S. IKEMOTO[1];
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**Abstract:** The ability to efficiently process information and make decisions is critical for animal survival during constantly changing environments. Medial septum (MS) has long been implicated in motivated behavior, although precise functions have not yet been identified. One

major issue of previous studies was that manipulations were not selective. The MS contains different cell types, including GABAergic, cholinergic, and glutamatergic neurons. GABAergic neurons are the most numerous. We sought to understand the roles of MS GABAergic neurons in motivated behavior. Although we previously reported that optogenetic stimulation of MS vGAT (GABAergic) neurons does not reinforce behavior, recent work reported that the stimulation of GAD2 GABAergic neurons induces real-time place preference. Therefore, we hypothesized that only a subset of MS GABAergic neurons may respond to rewarding stimuli. To confirm this, we injected vGAT-Cre and GAD2-Cre mice with AAV5-syn-FLEX-rc[ChrimsonR-tdTomato] and placed the animal in an ICSS task 2 weeks later. We found that GAD2-cre mice rapidly learned to lever press for stimulation, while vGAT-Cre mice did not. To understand the natural functions of MS GAD2 neurons, we used fiber photometry calcium imaging to detect MS GAD2 neuron activity during mice performed Pavlovian conditioned responses with water and footshock. AAV9-syn-FLEX-jGCaMP7f-WPRE was injected in GAD2-Cre mice, and a probe implanted into the MS. Mice were presented with three different tones paired with a 100%, 50%, or 0% chance of receiving water or a foot shock. We found that conditioned tones predicting water and water decreased the activity of MS GAD2 neurons (n=6). Conversely, conditioned tones predicting footshock and footshock increased the activity of MS GAD2 neurons. In addition, GAD2 neurons responded to the presentation of bright light or loud noise. These results suggest that positive stimuli inhibit MS GAD2 neurons, while negative stimuli excite them, and the pattern of the results is paradoxical given the finding that the stimulation of MS GAD2 neurons serves as a positive stimulus, reinforcing behavior. We are currently testing the hypothesis that MS GAD2 neurons enable mice to actively cope with the type of stimuli that trigger stress responses.

**Disclosures:** **C. Calva:** None. **J. Coudriet:** None. **S. Ikemoto:** None.

**Poster**

**PSTR040. Neuronal Circuits, Motivation, and Emotion**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR040.16/II28

**Topic:** G.03. Motivation

**Support:** NIDA R21 DA052594
T32 DA7281

**Title:** The effect of glucocorticoid receptor knockdown in a corticostriatal circuit on cue-motivated behaviors

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**Abstract:** The glucocorticoid receptor (GR) has been implicated in the pathophysiology of several psychiatric disorders such as impulse control disorders and substance use disorder. The mechanism by which GR impacts behaviors relevant to psychiatric disorders in the absence of external stress remains to be determined. We postulate that the involvement of GR in psychiatric disorders is due to the role it may play in mediating individual differences in the propensity to attribute incentive salience to a reward-paired cue. When a lever-cue is repeatedly paired with food delivery, sign-tracker rats (STs) assign predictive and incentive salience to the lever-cue, whereas goal-tracker rats (GTs) assign only predictive value to the cue. Additionally, it has been reported that, relative to GTs, STs are more impulsive on tasks assessing impulsive action, have attentional deficits, and are more likely to exhibit cue-induced reinstatement of drug-seeking behavior. These findings indicate that STs lack inhibitory control over their behavior. Inhibitory control is believed to derive from the cortex, at least in part, via its "top down" connections to reward-processing centers. Here, we assess the effect of GR knockdown in neurons of the prelimbic cortex (PrL) that have glutamatergic afferents to the nucleus accumbens core (NAcC). To achieve knockdown, we used Sprague Dawley transgenic rats of both sexes that contain flox sites on the 3$^{rd}$ exon of the GR gene (fl/fl; n=24). As Cre-mediated recombination results in GR knockdown, we used a dual viral vector approach to specifically knockdown GR within the PrL-NAcC circuit. Thus, floxed rats and their wildtype counterparts (wt/wt; n= 14), received an infusion of EF1a-fDIO-Cre in the PrL and EF1a-Flpo in the NAcC and subsequently underwent PavCA to evaluate their propensity for incentive salience attribution. Post surgical behavior of wt/wt rats was compared to fl/fl rats. GR knockdown within the PrL-NAcC pathway appears to increase the propensity to sign-track regardless of sex. In both males and females, GR knockdown resulted in a significant increase in sign-tracking behavior when compared to wt/wt controls ($F_{1,37} = 5.78$, $p=0.021$). This behavior remained apparent across all PavCA sessions. These results are pending circuit specific knockdown of GR via immunofluorescence. These findings suggest that GR within this top-down corticostriatal circuit acts to inhibit the tendency to attribute incentive motivational value to reward cues and resultant behaviors related to impulse control.

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**Poster**

**PSTR040. Neuronal Circuits, Motivation, and Emotion**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR040.17/JJ1

**Topic:** G.03. Motivation

**Support:** JSPS KAKENHI Grant Number JP20H05955
JSPS KAKENHI Grant Number JP23K12943

**Title:** Functional heterogeneity along the anterior-posterior axis of the primate ventral striatum revealed by chemical inactivation.

**Authors: *H. IWAOKI**, Y. HORI, E. KIKUCHI, Y. HORI, Y. NAGAI, M. HIGUCHI, T. MINAMIMOTO;
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**Abstract:** The ventral striatum is recognized as a key brain region for the processing of reward and motivation and has been implicated in the pathophysiology of psychiatric disorders such as obsessive-compulsive disorder (OCD). While research in rodents has suggested the existence of functional and anatomical differences within the anterior and posterior segments of the ventral striatum, it remains unclear whether such heterogeneity also exists in primates. To address this issue, we examined the behavioral effects of local blockade of neuronal transmission at mirror-symmetric sites along the anterior-posterior axis of the ventral striatum in two male rhesus monkeys. This inhibition was achieved by local injection of a GABAA agonist muscimol (3 µg/µl, 2 µl/site) using CT-MRI imaging guidance. Behavioral effects were assessed in two contexts: free movements in a cage and motivational behavior. In the free-moving context, anterior injections reduced activity and increased resting time in the cage compared to control sham injections. On the other hand, posterior injections resulted in hyperactivity and the manifestation of atypical behaviors, such as pecking at the corners of the cage. Motivational behavior was assessed using a reward-size task, in which the monkeys had to perform a simple bar release to earn juice rewards (1 to 8 drops) indicated by visual cues at the beginning of each trial. The error rates, which reflect the subjects' estimation of incentive-value and motivational state, were used as a measure of motivational behavior. Anterior injections did not alter the error rate but reduced the number of trials completed compared to the control. Conversely, posterior injection increased the error rate while leaving the number of trials completed unaffected. These results and hierarchical clustering analyses showed that these behavioral dichotomies emerged consistently in both contexts, depending on the anterior-posterior position of the injection, and were also consistent between the two monkeys. Our results provide evidence that functional heterogeneity along with the anterior-posterior axis is also present in the primate ventral striatum, which has important implications for understanding the neural network mechanisms underlying such functional heterogeneity and its relationship to clinical symptoms, especially in OCD cases.

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**Poster**

**PSTR040. Neuronal Circuits, Motivation, and Emotion**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

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**Topic:** G.03. Motivation

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**Title:** Epigenetic profiling of habit formation in mice subjected to chronic corticosterone administration

**Authors: *M. D. MURPHY**[1], K. S. KRICK[1], S. ZHANG[1], E. A. HELLER[2];
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**Abstract:** The dorsal striatum is a critical brain region for learning, decision-making, and motivated behaviors. Stress is a common abiotic factor that dysregulates many mammalian behaviors, including decision-making, learning, and memory. Corticosterone (CORT) activates the primary stress receptor, glucocorticoid receptor (GR), producing neuroendocrine changes which underlie stress pathology. However, the effects of CORT and GR activation on the neuronal epigenome and how this affects learning and motivated behaviors remain unknown. To characterize these effects, we chronically expose mice to CORT and subject mice to an operant training paradigm. This learning paradigm allows us to contrast limited and extended training periods to study how motivated behaviors become inflexible over time. We then profile dorsal striatum expression and post-translational histone modifications using RNA-seq and ChIP-seq, respectively, through operant training with and without CORT. We find that CORT produces some similar and some sex-specific differential gene expression and histone modification enrichment at plasticity genes, which may predispose sex-specific patterns of inflexible decision-making.

**Disclosures: M.D. Murphy:** None. **K.S. Krick:** None. **S. Zhang:** None. **E.A. Heller:** None.

**Poster**

**PSTR040. Neuronal Circuits, Motivation, and Emotion**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR040.19/JJ3

**Topic:** G.03. Motivation

**Support:** DA048280

**Title:** Aversion encoding by nucleus accumbens medium spiny neuron populations

**Authors: *B. E. COTE**[1], D. S. WHEELER[1], E. M. GRAFELMAN[1], L. VLACH[1], J. R. MANTSCH[2], M. C. HEARING[1], R. A. WHEELER[1];
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**Abstract:** More than 90% of the neurons in the nucleus accumbens (NAc) are GABAergic medium spiny neurons (MSNs) that express either D1- or D2-like dopamine receptors (DRD1

and DRD2), while approximately 5% express both. These NAc neuronal subtypes have been thought to exert opposing influences on behavior, as DRD1 MSN activity has been associated with reward-related behavior, while DRD2 MSN activity has been associated with aversion. However, recent studies suggest that this view may be overly simplistic. Stimulated DRD2 MSN activity has been found to increase reward-related behaviors, and DRD1 and DRD2 MSNs have been found to respond similarly to rewarding and aversive stimuli. To investigate how innately aversive experiences are encoded by NAc MSNs, we measured calcium activity in NAc MSN subpopulations using fiber photometry. Adora2 Cre+ mice (n=3) were injected with the calcium sensor, GCaMP6f in the NAc core as well as a chronically-implanted optic fiber. After allowing sufficient time for viral expression, mice were tested in daily sessions in which they were intermittently exposed to an aversive 90db white noise, and a milder 72db white noise (7db above ambient noise) presented in the same manner on alternating days. White noise was presented for 10 sec (20 presentations/session in a pseudorandom schedule with ITIs ranging from 50 to 90 seconds while *in vivo* calcium activity was recorded. Photometry recordings were aligned to stimulus onset and white noise-induced calcium activity changes were analyzed. Results indicate that DRD2 MSN calcium activity significantly increased at the onset of the aversive white noise ($t(2)=6.49; p<0.05$) while the less aversive noise did not significantly change activity ($t(2) =2.35; p>0.05$). This pattern of results aligns with the hypothesis that DRD2 MSN activity encodes aversive experiences. Ongoing experiments are comparing these findings with *in vivo* DRD1 MSN activity in response to white noise. Additionally, previous work from our lab has found that aversive stimuli (including 90db white noise) cause significant reductions in NAc dopamine. To understand the relationship between this dopamine signal and the MSN response to aversive stimuli, ongoing experiments using patch-clamp slice electrophysiology are examining how DRD1 and DRD2 MSN activity is modulated by different concentrations of dopamine. Together, this work will further our understanding of the mechanism by which aversive experiences are encoded by MSN subtypes in the nucleus accumbens.

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**Poster**

**PSTR040. Neuronal Circuits, Motivation, and Emotion**

**Location:** WCC Halls A-C

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**Topic:** G.03. Motivation

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ICREA, ICREA Academia 2018
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**Title:** Lay it on me: electrophysiological evidence from a newly developed social incentive delay task using personalized stimuli adapted from Instagram

**Authors: *S. NICOLAOU**[1,2], D. VEGA MORENO[2], J. MARCO-PALLARÉS[1];
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**Abstract:** Despite a growing interest in social reward and social punishment, existing studies are constrained by the challenges of replicating real social interactions in the laboratory. However, with social interactions increasingly taking place online, a more ecological approach would be to use stimuli adapted from popular social media platforms such as Instagram. To address this, we developed a novel electroencephalography-compatible social incentive delay task, which was implemented in thirty healthy young adults ($M_{age}$ = 23.03, *SD* = 3.03, 70% females) as they viewed a photo from their own or other participants' Instagram account, followed by a cue indicating the potential to see a positive (reward condition) or a negative comment (punishment condition) about the photo. After the cue, participants had to respond as quickly as possible to a target to receive a "Like" followed by a positive comment in reward conditions and avoid a "Dislike" followed by a negative comment in punishment conditions. Participants were led to believe that the comments were written by an external group of young people that evaluated their photos a week prior to the experiment. Reaction times to the target were significantly slower for punishment than for reward cues, but only on trials where participants viewed their own photos. This pattern suggests a response slowdown to see the negative comments, and it is consistent with participants' higher levels of curiosity to see the negative comments for their own (*M*= 8.21, *SD* = 2.22) than for other participants' photos (*M*=5.34, *SD* = 3.01). In line with the behavioral results, participants showed an increased Feedback-P3 Event-Related Potential when they received a "Dislike" on their own photos compared to the other conditions, indicating heightened salience of negative feedback. Interestingly, receiving a "Dislike" on participants' own photos also evoked the highest midfrontal theta oscillatory power compared to the other conditions, coherent with an increasing number of studies suggesting that theta power is involved in the processing of cues that convey social threat. Overall, results align with recent studies emphasizing the attention-grabbing nature of negative comments on social media, and most importantly, they also provide evidence for the incentive salience hypothesis in the digital era, which posits that it is possible to feel a strong motivational urge for information, even if there is no anticipated hedonic experience upon receiving that information.

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**Poster**

**PSTR040. Neuronal Circuits, Motivation, and Emotion**

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**Topic:** G.03. Motivation

**Support:** BBRF Young Investigator Grant

**Title:** Reward anticipation and information seeking as a transdiagnostic target in psychopathology.

**Authors: *P. SEPULVEDA**[1,3], Y. FARHAN[1,3], A. PHADNIS[4], I. AITSAHALIA[1], K. IIGAYA[1,3,2];
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**Abstract:** An influential idea in behavioral economics is that people derive pleasure from the moments leading up to a reward in addition to the reward itself (anticipatory utility, Loewenstein, 1987). Recent studies integrating a computational model of reward anticipation with an established information-seeking paradigm (Bromberg-Martin and Hikosaka, 2009) have suggested that humans prefer to obtain advanced information about future outcomes to enhance their experience of anticipation (Iigaya et al., 2016; 2020). However, to our knowledge, this anticipatory utility framework has not been applied to understand psychiatric conditions. In this work, using a transdiagnostic approach, we validate the suitability of the information and reward anticipation task across self-reported psychopathology in a large sample of online participants. In a web-based version of the task we developed, participants were first informed in each trial about the time delay prior to the delivery (or lack thereof) of a video reward. Participants could then choose to either receive immediate information or opt to remain uninformed about the upcoming result. Visual cues reflecting that choice, by either communicating or withholding the future outcome, would then remain onscreen for the duration of the delay; participants experienced the delay irrespective of the choice they made. In our setup, rewards were compelling videos in participants' preferred category (e.g., cute puppies), allowing for immediate consumption upon delivery. Participants displayed a wide range of information-seeking patterns. We found that participants who preferred to obtain advanced information about the outcome self-reported higher levels of anticipatory pleasure in established questionnaires. In a factor analysis that separated relevant psychopathology dimensions across multiple questionnaires, we found that higher expression of an Apathy-Anhedonia dimension was present in participants with lower information-seeking preference in the anticipation task. Our findings suggest that this new approach can offer quantitative behavioral measures for reward anticipation (RDoC construct) deficits, commonly expressed across clinical populations.

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**Poster**

**PSTR040. Neuronal Circuits, Motivation, and Emotion**

**Location:** WCC Halls A-C

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**Topic:** G.03. Motivation

**Support:** NIH-NIAAA T32AA026577

**Title:** Brain stimulation reward supports high discriminability and stable responding in an effort-based progressive ratio task

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**Abstract:** Progressive ratio (PR) tasks are used to quantify the effort subjects will expend to obtain a reward. In this task, the number of operant responses required to obtain each subsequent reward escalates until they reach the break point, where rats no longer exert the required effort. Break point depends on reward quality and schedule difficulty. PR tasks typically use food, water, or drugs as rewards, the value of which may be confounded with satiety or tolerance. Instead, brain stimulation reward (BSR) acts as a non-satiating, tolerance-resistant reward. We hypothesized performance on a BSR-reinforced PR task would depend on both schedule difficulty and reward stimulation frequency without the need for food restriction to motivate behavior or the confound of satiation in determining break point. Once the minimal reinforcing stimulation amplitude was determined for each subject they were trained to stable performance on a rate frequency task to identify threshold (theta) and maximum responding (alpha) frequencies. Reward frequencies for PR were calculated as 95%, 50%, and 25% of alpha, which were shown to be highly discriminable. Rats were tested on the PR task using three reward levels (95%, 50%, or 25% of alpha) and two schedules (low or high effort). For any given reward level, rats earned significantly more rewards for the low compared to the high effort schedule. However, break point occurred at fewer cumulative presses on the low effort schedule. Comparing across reward frequencies and schedules, we saw no difference in the number of rewards obtained for 95% and 50% reward level. However, rats obtained fewer rewards on both schedules for the 25% reward.Overall, we found BSR to act as a non-satiating and highly stable reward when used in PR responding. The use of BSR in PR tasks avoids issues with other reinforcers while supporting a high level of discrimination and motivated behavior.

**Disclosures: J.P. Sevigny:** None. **R.M. Donka:** None. **J.D. Roitman:** None.

**Poster**

**PSTR040. Neuronal Circuits, Motivation, and Emotion**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR040.23/JJ7

**Topic:** G.03. Motivation

**Title:** Reward rate modulates movement vigor: insights during DBS ON and OFF conditions

**Authors: *M. E. TIEMEYER**[1], M. E. ALARIE[2], G. PAGNIER[3], W. F. ASAAD[4];
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**Abstract:** The basal ganglia (BG) have been widely associated with controlling motor actions and reward perception. Dopamine (DA) is known to modulate these behaviors, where movement vigor is directly influenced by the degree of perceived reward. This is especially relevant in the case of Parkinson's Disease (PD) in which low DA levels reduce patients' motor ability. Lowered DA levels also impact the encoding of reward prediction errors. DA neurons in the midbrain are activated when a presented reward is greater than predicted. Events that signal this positive reward prediction error are thought to modulate movement vigor through a transient increase in DA release, although this relationship is poorly understood. Multi-armed bandit tasks have been widely implemented to understand reinforcement learning and the exploration-exploitation tradeoff - a dilemma that decision-makers face when balancing between exploring uncertain choices and maximizing reward. Here we report data from a motoric two-armed bandit task, comparing outcomes across healthy controls and patients with subthalamic nucleus (STN) deep brain stimulation (DBS) to treat PD. We investigate the influence of choosing between high and low rewarding options on movement vigor. Participants quickly learn which is the optimal bandit, as measured by changes in choices and movement speed. Furthermore, a central question we have addresses whether STN DBS modulates this learning process. This task implements "forced-choice" trials in which participants are required to choose one of the bandit options. These forced-choice trials ensure that the less rewarding target is still selected even after learning occurs, permitting deeper insights into the role of reward on movement speed. Indeed, we predict movement times between bandits to be comparable pre-learning but different once participants learns the optimal bandit to choose. Preliminary results suggest that movement speed is slower with a lower previous reward compared to movement times after moderate and high rewards. Overall findings from this study will ultimately expand our understanding of how the BG serves as a central hub in the integration of reward perception and motoric movement.

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**Poster**

**PSTR040. Neuronal Circuits, Motivation, and Emotion**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR040.24/JJ8

**Topic:** G.03. Motivation

**Support:** NIH Grant R01DA044199

**Title:** Deep exploration of sign-tracking behaviors in dynamic cue-reward relationships

**Authors: *E. S. TOWNSEND**, D. GARROD, K. S. SMITH;
Dartmouth Col., Hanover, NH

**Abstract:** Reward predictive cues can acquire their own motivational value. The physical manifestation of this motivation is often cue-triggered Pavlovian conditioned approach,

commonly referred to as sign-tracking. In dynamic environments, inflexible responding to reward cues may become detrimental, suggesting that behavior should be sensitive to these environmental changes and flexibly adjust. Indeed, sign-tracking has been previously shown to flexibly change after introduction of an omission schedule, where deflection of a lever-cue cancels delivery of the reward (Chang and Smith, 2016). Conversely, sign-tracking is historically known to be quite persistent in situations such as extinction, in which cues are no longer paired with rewards. It is unknown how animals adjust their sign-tracking responses to accommodate—or remain persistent—in response to new cue information. To address this, the microstructure of cue-evoked behavioral responses (rather than lever pressing alone) in sign-tracking animals during omission, extinction, and reacquisition schedules were evaluated. Altogether, our results allow for deeper exploration of dynamic and naturalistic motivation that goes beyond traditional measures of sign-tracking (i.e., lever presses). Further, we parse out deeper phenotypes and individual differences in persistence and flexibility of cue attraction and motivation.

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**Poster**

**PSTR040. Neuronal Circuits, Motivation, and Emotion**

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**Program #/Poster #:** PSTR040.25/JJ9

**Topic:** G.03. Motivation

**Support:** DA047102

**Title:** The fundamental relationship between motivation and frustration

**Authors: *Y. M. MARMOL CONTRERAS**, P. SHAH, T. A. GREEN;
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**Abstract:** Despite extensive knowledge of the link between frustration and substance use disorders tracing back as early as the 1940s, there is not much research assessing the role of frustration in motivation-related disorders. In recent years, a novel model for quantifying frustration-related behavior has enabled us to study motivation- and frustration-related behavior simultaneously in real time by measuring barpress durations during operant tasks. In this study, we employ this novel tool to explore the fundamental relationship between motivation and frustration. Our previous work showed that frustration affects motivation, but the question of motivation affecting frustration had not yet been sufficiently explored. To this end, we used satiety-based devaluation strategies to manipulate motivation and resulting frustration-related behavior for sucrose pellets was assessed. In some cases, we were able to affect motivation without changes in frustration-related behavior, but in other cases, changes in motivation also affected frustration. Differential effects were contingent upon factors such as length of session and reward size.

**Disclosures:** **Y.M. Marmol Contreras:** A. Employment/Salary (full or part-time); UTMB. **P. Shah:** A. Employment/Salary (full or part-time); UTMB. **T.A. Green:** A. Employment/Salary (full or part-time); UTMB.

**Poster**

**PSTR041. Motivation: Higher Cognitive Processing**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR041.01/JJ10

**Topic:** G.03. Motivation

**Support:** NIH Grant DA055202-01

**Title:** Gonadal hormone modulation of pain-induced impulsivity and response to morphine in rats

**Authors: *A. TSENG**, E. E. FELIX, N. ESPINOZA SERRANO, A. NAZARIAN;
Dept. of Biotech. and Pharmaceut. Sciences, Col. of Pharm., Western Univ. of Hlth. Sci., Pomona, CA

**Abstract:** Impulsivity is characterized by a deficit in planning and making choices for immediate gratification with reduced concern for long-term negative outcomes. While impulsivity is a personality trait encompassing a normal spectrum among healthy individuals, an excess of impulsive choices is associated with a wide range of maladaptive behaviors and adverse life events. Patients with chronic pain show higher impulsivity, and this is associated with the development of psychiatric comorbidities including anxiety and depression as well as a higher risk for the misuse of prescription opioids. It is therefore important to understand the mechanisms underlying pain-induced impulsivity to better treat chronic pain and its associated manifestations. Previously, we showed that female rats with persistent inflammatory pain were more impulsive compared to male subjects. The goal of the present study was to determine the role of gonadal hormones on sex differences in pain-induced impulsivity. Male and female Sprague-Dawley rats underwent gonadectomy. Persistent inflammatory pain was induced by hind paw injection of complete Freund's adjuvant (CFA). Impulsivity was measured using a delay discounting task in which rats were given a choice between a lever providing a small amount of food delivered immediately or one providing a larger amount of food delivered after a delay. Rats were categorized as either high- or low-impulsive according to their baseline response. To test the effect of gonadal hormones, rats were supplemented with 17-beta-estradiol or testosterone, given via subcutaneous injection at a dose and schedule meant to represent physiological levels. In high-impulsive males, gonadectomy decreased impulsivity, while in low-impulsive males gonadectomy had no effect. CFA treatment gradually heightened impulsivity in high- and low-impulsive male rats regardless of testosterone supplementation. Morphine blocked CFA-induced impulsivity in rats that were given testosterone; however, this effect was blunted in the castrated rats that did not receive hormone replacement. In female rats, ovariectomy did not alter baseline impulsivity, while CFA treatment enhanced impulsivity over time. The effect of

CFA was similar in groups that did or did not receive estradiol replacement. Morphine blocked the pain-induced impulsivity in both ovariectomized rats as well as those receiving hormone supplementation. These results suggest that gonadal hormones contribute to baseline and pain-induced impulsivity and that these effects may be sexually dimorphic.

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**Poster**

**PSTR041. Motivation: Higher Cognitive Processing**

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**Topic:** G.03. Motivation

**Support:** NIH Grant R15MH125282

**Title:** The effects of peripartum estradiol fluctuations on nucleus accumbens dopamine dynamics in mice

**Authors: J. M. MAURICE**[1], A. R. HALLIDAY[1], M. Y. COURTNEY[1], L. E. CRAIG[1], K. SAMSON[2], R. A. ESPAÑA[2], *L. E. BEEN[1];
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**Abstract:** The peripartum period produces dramatic hormonal changes. In mammals, estradiol levels increase up to 100-fold during late pregnancy, but rapidly drop to pre-pregnancy levels after birth. The resulting postpartum estradiol withdrawal state is believed to play a role in the etiology of postpartum mood and anxiety disorders, which affect approximately 1 in 8 birthing people. Previous research in our lab and others has shown that postpartum estradiol withdrawal affects the nucleus accumbens (NAc) and motivated behaviors. However, specific neural mechanisms connecting peripartum estradiol fluctuations to brain and behavioral changes are not well understood. We therefore used a hormone-simulated pseudopregnancy (HSP) in adult female C57BL/6 mice to model postpartum estradiol withdrawal and subsequently characterized mesolimbic dopamine dynamics in the NAc core with ex-vivo fast-scan cyclic voltammetry (FSCV). Adult female mice were ovariectomized and given daily hormone injections that simulate estradiol levels during pregnancy. In one group of mice (n = 5), estradiol was withdrawn following HSP, simulating the rapid drop in estradiol during the postpartum period. In another group (n = 5), estradiol levels were sustained at high levels after HSP. Both groups were compared to a control group (n = 5) that received vehicle injections throughout the duration of the experiment. Five days after the mice were split into withdrawn or sustained conditions, they were euthanized and dopamine release and reuptake were measured with FSCV. We found that sustained high-dose estradiol administration during the simulated postpartum period decreased dopamine release and reuptake rate in the NAc core compared to mice who were withdrawn from estradiol or vehicle controls. Ongoing experiments aim to replicate these

findings and draw connections between peripartum estradiol fluctuations, mesolimbic dopamine dynamics, and behavioral changes.

**Disclosures:** **J.M. Maurice:** None. **A.R. Halliday:** None. **M.Y. Courtney:** None. **L.E. Craig:** None. **K. Samson:** None. **R.A. España:** None. **L.E. Been:** None.

**Poster**

**PSTR041. Motivation: Higher Cognitive Processing**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR041.03/JJ12

**Topic:** G.03. Motivation

**Support:** Undergraduate Biology Research Program
NSF Grant 1703340

**Title:** Rats may use different information to locate a positive or negative unmarked area in an open field

**Authors: J. WIELAND**[1], A. KEEN[1], *J.-M. FELLOUS[2];
[1]Undergraduate Biol. Res. Program, [2]Univ. of Arizona, Tucson, AZ

**Abstract:** Most rodent navigation tasks use of cue-rich reward areas to encourage learning or adverse stimuli such as electrical foot shocks to elicit place avoidance. However, rats can also learn to enter and avoid unmarked areas that trigger future rewards or punishments. Both reward and avoidance locations have been shown to influence the properties of hippocampal place fields. Many studies have also shown that the spatial navigation circuits of the hippocampus are influenced by inputs from the medial (MEC, self-motion, path integration) and the lateral (LEC, sensory processing including landmarks and cues, local frame of reference) entorhinal cortices. We focused on the roles of visual cues on the ability to interact with unmarked local (no cue, no boundary) positive and weakly cued (no boundary, small mark on the floor) negative zones on a circular open field arena. When the rat entered the positive unmarked zone, it was rewarded at a random feeder on the circumference of the arena, away from the zone. When the rat entered the negative zone, the feeder that was cued was de-activated and a delay was initiated before another reward location became active.
Each experimental session was divided into two epochs, baseline and manipulation. During baseline, a cue on the arena wall and a distal cue on the curtain surrounding the arena were associated with the zone. During the manipulation, 3 conditions were tested: the cues and the zone moved together; the cues moved, but the zone remained unchanged; or the zone moved, and the cues remained unchanged.
Rats learned to enter the positive zone in both the baseline and manipulation epochs for all conditions. During manipulation, when moving the zone to a new location unassociated with the cue, the rat would enter the zone that was active during baseline more often than any control zones. However, this effect was not significant in the condition when only the cue was moved.

During the baseline section, the rats learned to avoid the negative zone by gradually adjusting their trajectories around it. Rats were able to navigate more accurately and avoid the negative zone when the cues and zone moved together, but less so when the cues and zone were moved independently. However, they still learned and avoided the negative zone more than the control zones during the manipulation epoch.
These results suggest that rats did not significantly rely on visual cues to locate an unmarked positive zone. However, the added floor cue in the negative condition did significantly affect navigation. Rats therefore may predominantly use self-motion (MEC inputs) in positively motivated conditions and sensory perception (LEC inputs) in negatively motivated conditions.

**Disclosures:** **J. Wieland:** None. **A. Keen:** None. **J. Fellous:** None.

**Poster**

**PSTR041. Motivation: Higher Cognitive Processing**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR041.04/JJ13

**Topic:** G.03. Motivation

**Title:** Novel Behavioral Measurements of Social Motivation in Mice: Comparison Across Sex and Strain

**Authors: I. RAMOS**[1], S. BROWN[1], F. RAZZAQ[1], K. PERSSICO[1], *T. ROGERS[2];
[2]Psychology Dept., [1]Middle Tennessee State Univ., Murfreesboro, TN

**Abstract:** While behavioral measures for general social exploration in mice are established, few measurements exist for social motivation. Social motivation differs from social exploration as the animal subject must exert effort to access a presented social stimulus (another mouse). We have created two novel behavioral tasks to measure social motivation in mice. The first task, the weighted doors task (adapted from Borland et al., 2017, *J Neurosci Methods*), requires mice to push open a one-way swinging door to access a social stimulus. The door is first unweighted and weights are then added to the door with each successive trial to increase the difficulty to access the social stimulus. The second task, the ladder task, requires mice to climb a ladder to access a platform containing a social stimulus. The height of the platform and angle of the ladder is successively increased with each trial. All social stimuli used in our tasks were same-sex, same-strain, age-matched, weight-matched conspecifics. All subject mice were evaluated for motor skill, reflexes, and general health to identify any confounding variables in behavioral results. To validate the novel social motivation behavioral tasks, we measured behavioral outcomes across multiple measurements of social motivation, correlated outcomes across these measures, and compared these social motivation measurements with classic social exploration tasks. Additionally, we compared behavioral outcomes across sex (male, female) and across three mouse strains (C57, DBA, and BTBR). We found statistically significant positive correlations within social motivation tasks ($r = 0.58$, $n = 31$, $p < 0.001$). Social motivation measures were not correlated with sociability as measured by the three-chamber task (ladder task: $r = -0.11$, $p >$

0.05; weighted doors: r = -0.29, p > 0.05). A mixed methods ANOVA indicated that sex was not a significant variable in social motivation variability as measured by the ladder task or weighted doors task, but that strain had a significant effect on social motivation in both tasks (ladder task: $F(2, 45 = 19.02$, $p < 0.001$; weighted doors: $F(2, 41) = 13.08$, $p < 0.001$). These novel measurements of social motivation allow for the investigation of unique neurochemical and/or neural pathway contributions to social motivation. Specifically, the roles of neuromodulators such as oxytocin, which has variable social behavior impacts in both rodent models and humans, may be further elucidated by more specific social behavior measurements.

**Disclosures: I. Ramos:** None. **S. Brown:** None. **F. Razzaq:** None. **K. Perssico:** None. **T. Rogers:** None.

**Poster**

**PSTR041. Motivation: Higher Cognitive Processing**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR041.05/JJ14

**Topic:** G.09. Drugs of Abuse and Addiction

**Title:** Evaluation of cognitive function in male and female mice using the Feeding Experimentation Device v3 (FED3)

**Authors: *L. B. MURDAUGH**[1,2], B. BROWN[2], C.-H. CHEN[2], Y. DONG[2], C. MILIANO[2], S. SHEPARD[2], S. VIJAYAN[2], A. GREGUS[2], M. W. BUCZYNSKI[2];
[1]Translational Biology, Medicine, and Hlth., [2]Sch. of Neurosci., Virginia Tech., Blacksburg, VA

**Abstract:** Background: Measuring cognitive behaviors are important for many neuroscientific disciplines, but large-scale studies can be hampered by the prohibitive cost of traditional operant behavioral apparatuses and the time needed to run large mouse cohorts. Here, we develop a protocol using the open-source Feeding Experimentation Device version 3 (FED3) to assess multiple aspects of cognitive performance in male and female mice. To validate the protocol, we first investigated response-reward contingency on operant performance. Next, we ascertained construct validity of a cognitive flexibility task using orbitofrontal cortex lesions, as this region is known to impact Reversal Learning (RL) while sparing Discrimination Learning (DL). Finally, we demonstrated feasibility by measuring cognitive deficits in mice with the P129T Fatty Acid Amide Hydrolase (FAAH) mutation, which is associated with problem drug use and addiction-like behaviors.

Methods: Mice were food restricted to 16h/day in group-housed home cages, and each mouse has a dedicated testing cage for the 8h sessions with the FED3 as the only food source. All testing was performed during the animals' dark cycle. Response-reward contingency and operant performance was measured in adult C57BL6/J males during 8h sessions of Free Feeding or Fixed Ratio (FR) reinforcement schedules. Construct validity of the DL/RL task was performed in adult C57BL6/J males with ibotenic acid lesions or sham controls. Aged (150+ days) P129T KI

and WT males and females were run through a behavioral test battery consisting of DL/RL, Progressive Ratio, and punished intake (via quinine adulterated pellets), and extinction and reinstatement.

Results and Discussion: Initial findings demonstrate that genotype (wild-type versus P129T KI) had no significant effects on performance during DL or RL, though there were main effects of sex on DL acquisition. Additionally, there were no main effects of sex or genotype on Quinine consumption or Reinstatement. But KI animals consumed significantly fewer pellets before breakpoint during the Progressive Ratio task and made significantly fewer pokes on the first day of Extinction. Together, these results demonstrate the FED3 is a valid alternative to traditional operant chambers which can be used to measure operant behavior in large cohorts of animals.

**Disclosures: L.B. Murdaugh:** None. **B. Brown:** None. **C. Chen:** None. **Y. Dong:** None. **C. Miliano:** None. **S. Shepard:** None. **S. Vijayan:** None. **A. Gregus:** None. **M.W. Buczynski:** None.

**Poster**

**PSTR041. Motivation: Higher Cognitive Processing**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR041.06/JJ15

**Topic:** H.03. Decision Making

**Support:** Arizona Alzheimer's Consortium
Arizona State University Start-up Funds

**Title:** Juvenile female mice demonstrate increased motivation and attention compared to middle-aged animals in a pairwise visual discrimination task

**Authors: V. TRUONG**[1], S. BOWSER[1], *J. VERPEUT[2];
[1]Psychology, [2]Arizona State Univ., Tempe, AZ

**Abstract:** Dementia-related illnesses are a proliferating concern for the healthcare industry as the population ages. While many studies track the rate of cognitive decline in later stages of dementia, there has been little research on rates of decline during early dementia. Determining differences in early cognitive decline between males and females will allow for better individualized healthcare and increased understanding of how cognition wanes across the lifespan. Additionally, focusing on sex differences is imperative to confirm whether neuroprotective hormones, such as estrogens and androgens, affect cognitive decline before and during the onset of dementia (Bimonte-Nelson, et al., 2021). We hypothesized that juvenile, postnatal day 21 (P21) female mice would exhibit equal performance to males, but would undergo less drastic cognitive decline than males into middle-age. Cognitive changes across the lifespan were examined in both male and female C57BL/6J juvenile (P21) and middle-aged (10 months old) mice (n = 12 per group) using a pairwise visual discrimination task. During this

task, animals learn to associate choice of one shape with a reward of sweetened condensed milk. After 10 days, the correct shape is switched to analyze reversal learning. We found that while juvenile male and female mice were able to discriminate between two shapes equally, female mice, regardless of age, were faster to initiate each trial ($p < 0.01$) and choose an image ($p < 0.001$). Juveniles initiated and responded faster to trials during early stages of shaping ($p< 0.05$). In addition, juveniles demonstrated significantly more correct choices during visual discrimination ($p < 0.05$), but no age differences were found for reversal learning. This current work establishes age-related changes in both males and females on the visual discrimination task, a translatable task to humans, which will be used to quantify changes in neural pathology and brain structure in future studies.

**Disclosures: V. Truong:** None. **S. Bowser:** None. **J. Verpeut:** None.

**Poster**

**PSTR041. Motivation: Higher Cognitive Processing**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR041.07/JJ16

**Topic:** F.07. Biological Rhythms and Sleep

**Support:** NSF CAREER Award 2142911

**Title:** Spiral waves are coordinated topographically across cortical and subcortical brain areas

**Authors: *Z. YE**[1], M. BULL[2], D. BIRMAN[1], A. LI[1], N. STEINMETZ[1];
[1]Univ. of Washington, Seattle, Seattle, WA; [2]Allen Inst. fro Brain Sci., Seattle, WA

**Abstract:** Spontaneous neural fluctuations including oscillations and traveling waves are prevalent in the brains of behaving mammals. Given the topographical connections between various brain areas, we hypothesized that these moment-to-moment neural fluctuations and traveling waves are coordinated across cortical and subcortical areas. Using widefield calcium imaging across the dorsal cortex of awake mice, we identified that 3-6 Hz oscillations are globally distributed, with highest power in retrosplenial and visual cortices. Traveling waves, including spirals, emerge during 3-6 Hz oscillations. Spiral waves are highly concentrated in the center of the somatosensory cortex (SSp), and we discovered that this activity pattern reflects a striking circular bias in the orientation of intracortical axons in this region. These activity patterns are coordinated between left and right hemispheres, as well as between anterior and posterior cortex, consistent with topographically organized connectivity linking these areas. Computational simulations with a Kuramoto model of weakly-coupled oscillators confirm that biased axonal connectivity in SSp and topographically connected maps can reinforce the development of spiral activity patterns. By measuring activity simultaneously across cortex and densely in subcortical areas including thalamus, striatum and midbrain, we observed that moment-to-moment cortical wave position and traveling direction were reflected in subcortical activity. Together, we have demonstrated that spiral waves are observed in the awake mouse

cortex, and that these waves are coordinated topographically across cortical and subcortical areas. Spatiotemporal coordination of traveling waves across the brain will inevitably modulate population neural dynamics, with fundamental implications for sequential behavior encoding to be elucidated.

**Disclosures: Z. Ye:** None. **M. Bull:** None. **D. Birman:** None. **A. Li:** None. **N. Steinmetz:** None.

**Poster**

**PSTR041. Motivation: Higher Cognitive Processing**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR041.08

**Topic:** G.03. Motivation

**Title:** Neural representations of curiosity in nonhuman primate prefrontal cortex

**Authors: *X. TIAN**[1], A. C. SILVA[2];
[2]Univ. of Pittsburgh, [1]Univ. of Pittsburgh, Pittsburgh, PA

**Abstract:** Curiosity is a well-known phenomenon in the psychology of motivation. Its innate, spontaneous drive reduces negative states and fosters learning and exploration that may reveal beneficial opportunities for growth and advancement. However, our knowledge of the brain circuits and neural underpinnings of curiosity is still incomplete. Our previous fMRI imaging study in marmosets (*Callithrix jacchus*) identified the prefrontal cortex as a primary contributor to curiosity (Tian et al., Cerebral Cortex 2021). We hypothesized that curiosity is an integrative process in which the serial prefrontal pathway plays an important role in balancing cognition and emotion. Here, we test this hypothesis by performing large-scale, high-density in-vivo electrophysiological recordings in the prefrontal cortex of one of the marmosets used in the previous study. We implanted a 128-channel matrix electrode in the prefrontal cortex of the marmoset subject and recorded neuronal activities as the animal performed the same curiosity-driven visual text described in (Tian et al., Cerebral Cortex 2021). Analysis of the ephys data revealed that: 1). Curiosity-driven behavioral performance could reflect from Prefrontal responses. 2). Neurons in the Prefrontal cortex could acquire information representations, and some exhibit presentations of the novel stimulus. 3). As an integration hub, the medial prefrontal cortex (mPFC) might balance the serial prefrontal pathway. Compared with other Prefrontal subregions, its activity can significantly drive or inhibit the execution of curiosity-related behaviors. All in all, our new results provide a new understanding of curiosity and facilitate future studies of neuroscience and psychology of curiosity.

**Disclosures: X. Tian:** None. **A.C. Silva:** None.

**Poster**

**PSTR041. Motivation: Higher Cognitive Processing**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR041.09/JJ17

**Topic:** C.01. Brain Wellness and Aging

**Support:** NIH Grant R01MH121706
NSF GRFP DGE-2137419

**Title:** Longitudinal study of social and non-social reward valuation in adolescent primate development: initial report

**Authors: *A. I. BOWMAN**[1,2], A. A. MORRISON[3], S. KIM[3], C. BOLLES[3], S. W. CHANG[5], K. M. GOTHARD[4,3,2];
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**Abstract:** During adolescence, humans develop higher tolerance for delayed rewards and acquire new prosocial behaviors. Tolerance for delayed rewards is measured by delay discounting tasks, whereas prosocial decision making can be tested by reward allocation tasks. The emergence of adult-like social and non-social behaviors depends on the successful remodeling of amygdalo-prefrontal circuits. The long-term goal of this project is to capture these behavioral changes and determine their neural underpinnings. As a first step, we measured the performance of 6 adolescent (ages 28-45 mo) and 2 adult (ages 8 yr) male rhesus macaques on a version of a delay discounting task in which subjects chose between an immediate, small reward (1 banana pellet) or a delayed larger reward (3 banana pellets) received after delays ranging from 0 to 25s. The delay increased gradually across sessions until the subject systematically chose the small immediate reward. An arctangent function was fitted to individual choice behavior to find the delay at which monkeys picked each reward option 50% of the time (indifference point). We found large individual variation in indifference points between the subjects (ranging from 7.4s to 17.3s) that did not correlate with age. Interestingly, indifference points were significantly lower (by 3.2 to 11.0s; $p = 0.0078$, Wilcoxon signed-rank test) when the delays gradually decreased across sessions, indicating that all monkeys, regardless of age, were less tolerant to delays after they experienced longer delays. To test for the emergence of prosocial behaviors, the same animals performed a reward allocation task in which they chose between rewarding only themselves or themselves and a pair-bonded partner in one context (self/both); and between rewarding only their partner or dispensing a reward into a container both participants can see (other/neither). Three of the four adolescents who have completed this task chose more frequently to give their partner a reward in both trial types. Eight months later, all four adolescents became significantly more other-preferring in the other-neither context, with two significantly preferring to reward themselves and their partner in the self/both context. Both tasks will be readministered at landmark stages of development and aligned to morphometric, endocrine, and ethological variables. Our findings so far suggest that age is not the sole predictor of delay tolerance. It is possible that macaques, unlike humans, develop adult-like discounting behavior very early in adolescence. Age, however, appears to be a good predictor of developmentally dependent increases in prosocial behavior.

**Disclosures:** **A.I. Bowman:** None. **A.A. Morrison:** None. **S. Kim:** None. **C. Bolles:** None. **S.W. Chang:** None. **K.M. Gothard:** None.

**Poster**

**PSTR041. Motivation: Higher Cognitive Processing**

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**Topic:** G.03. Motivation

**Support:** Special Research Fund Ghent University, Grant number BOF20-GOA-004
European Union's Horizon 2020 research and innovation program, Grant agreement 852570

**Title:** The neural dynamics involved in the translation of motivational signals to effort exertion

**Authors:** ***N. KUKKONEN**, S. BRAEM, S. MATTIONI, J. EAYRS, T. STEENDAM, M. CHAI, R. KREBS;
Exptl. Psychology, Ghent Univ., Gent, Belgium

**Abstract:** Effort is conceptualised as a decision-making problem: the inherent cost of effort is weighed against the incentives to expend effort. Effort allocation/preparation is based on this cost-benefit calculation. Until now, effort evaluation has not been systematically separated from the preparation stage where the aversive nature of effort is translated into invigoration to ensure successful task performance. Effort-based decision-making studies (where effort is not necessarily exerted after a decision about effort is made) have provided evidence of effort discounting of reward in the brain. However, effort-expenditure studies, where a cue informs participants of the reward and demand level of the upcoming task, uncovered that high demand can also motivate effort allocation. Most effort, as indexed by recruitment of neural structures underlying effortful control, is exerted in a high demand context when the incentive is high. In the present fMRI study we explored effort as a dynamic process involving both evaluation (decision-making) and allocation (preparation for task) in a within-participants study (n = 40, females and males) to reconcile the earlier, seemingly contradictory, findings in the effort literature. Human participants completed a speeded cognitive control task, alternating between four cueing conditions that differed in the incentive level (high vs. low reward) and demand level (easy vs. difficult). A trial began with an ‘evaluation cue’ (e-cue) that informed the participants of the condition, prompting evaluative processing of the upcoming effort condition. An e-cue was succeeded by an ‘allocation cue’ (a-cue), during which preparation for the coming task took place, followed by the actual task (5 targets in a row). Delta functions on the different cue and target onsets, depending on the four event types, were entered into a GLM. With this GLM, the whole-brain activity within the evaluation phase and the allocation phase were tested separately. By conceptualising effort as a multi-stage, dynamic process, we were able to tease apart stages of effort in evaluative and attentional control networks. We hope this operationalization of effort

provides researchers and clinicians a way to zoom in on the components of effort expenditure in both healthy and disrupted effortful behaviour.

**Disclosures:** **N. Kukkonen:** None. **S. Braem:** None. **S. Mattioni:** None. **J. Eayrs:** None. **T. Steendam:** None. **M. Chai:** None. **R. Krebs:** None.

**Poster**

**PSTR041. Motivation: Higher Cognitive Processing**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR041.11/JJ19

**Topic:** G.03. Motivation

**Support:** ISF Grant 1603/22

**Title:** The sensorimotor and cognitive determinants of perceived effort

**Authors:** ***N. WOLPE**, E. HERZBERG;
Tel Aviv Univ., Tel Aviv, Israel

**Abstract:** The way people perceive effort in everyday life is highly variable across individuals and can have significant implications for their mental health and overall well-being. For example, inflated perception of effort can lead to a withdrawal from goal-directed activities, as observed in people with low motivation or clinical apathy. Previous studies have examined how people value effort vs. reward when making decisions whether to act, and which action to choose. However, the features that make an action effortful remain unknown. Here, we sought to examine these features. Young adult participants (n=90) performed a computerised physical effort task. On each trial, they were asked to exert force using a hand dynamometer, so as to make 'mercury' in a visually displayed 'thermometer' reach a target zone for 3 seconds, within a 7-second time window. The target force magnitude on each trial was pseudorandomly selected from a set of forces {20%, 40%, 60%, 80%, 100%} relative to participant's maximum voluntary contraction, which was measured at the start of the experiment. After exerting the force, visual feedback was displayed indicating whether the participant successfully reached the target zone for the required time. Participants were then asked to rate their perceived effort on that trial using a 0-100 visual-analogue scale. Using a generalised linear mixed effect model, we found that people's effort perception on each trial was influenced by both across- and within-trial variables of the task. Specifically, across trials, target force (reflecting the goal), trial number (reflecting fatigue) and previous effort rating (perseveration) were positive predictors, while 'success' feedback (reward) and increased target force in the previous trial (force anticipation) were negative predictors. Within-trial, overall force everted and force variation were positive predictors, while initial force peak was a negative predictor of perceived effort. Our findings suggest multiple sensorimotor and cognitive features of an action that contribute to the experience of effort, over and above the action goal and work exerted. Individual differences in

these features may differentially contribute to clinical states of inflated effort perception such as apathy.

**Disclosures:** **N. Wolpe:** None. **E. Herzberg:** None.

**Poster**

**PSTR041. Motivation: Higher Cognitive Processing**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR041.12/JJ20

**Topic:** G.03. Motivation

**Support:** NIDA Intramural Research Program

**Title:** Characterizing sign tracking behavior in humans: a pilot study

**Authors:** *B. SALMERON[1], **E. THAO**[2], S. FOX[3], K. NOEMER[3], T. J. ROSS[3];
[1]NIDA, Baltimore, MD; [2]Natl. Inst. of Drug Abuse, Baltimore, MD; [3]Natl. Inst. on Drug Abuse, Baltimore, MD

**Abstract:** In classical conditioning experiments, sign tracking (ST) places motivational and reward value on the conditioned stimulus (CS). Goal tracking (GT) describes using the CS to obtain the reward without attributing value to the CS. ST is correlated with impulsivity, aggression, and poorer attention. Because GT and ST relate to motivation and response to reward, there are potential implications for substance use disorders. Limited preliminary studies show that eye-tracking can be used to measure ST vs GT in humans. We are developing a simple sign tracking task to explore the characteristics of sign tracking for both natural rewards and drug-related rewards in participants with tobacco and cocaine use disorder and healthy controls without requiring any special equipment. Here we present preliminary data on healthy controls (n=33 (17M)). We hypothesized that this ST task would identify a range of ST behavior in healthy controls. Images are presented on the screen for two seconds. If participants want to continue seeing the image, they must press a button at least once per second. Images can be viewed for an additional 13 seconds. If they stop pressing, a white plus sign will appear for the remainder of the time. Periodically, an image of $5 appears to monitor engagement with the task. Participants earn $5 if the keep the image up for the maximum time. Other images include liked foods (to assess motivational value of a cue without the possibility of the reward), disliked foods (to control for responding due to boredom), drugs (to compare ST for natural rewards and drug rewards). Before the task, participants are asked to rate a variety of foods on a scale of 1 to 9. The task selects the highest and lowest rated foods to present during the ST task. The task takes about 20-25 minutes to complete. It is scored based on number of button presses and the duration images are kept on the screen, corrected for disliked foods. The results showed that 84% of participants earned all $5 rewards, indicating high engagement with the task. Sign tracking behavior was evenly distributed from no ST (no button presses for pictures other than $5) to complete ST behavior (keeping all liked food images up for the maximum time allowed).

Healthy controls exhibited very little ST towards drug cues. These preliminary results show that the task succeeded in identifying ST in humans and that it behaves like a continuous variable. Our next steps are to assess the stability of ST behavior across time and to assess ST for natural and drug cues in individuals with cocaine use disorder or tobacco use disorder.

**Disclosures: B. Salmeron:** None. **E. Thao:** None. **S. Fox:** None. **K. Noemer:** None. **T.J. Ross:** None.

**Poster**

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**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR041.13/JJ21

**Topic:** F.07. Biological Rhythms and Sleep

**Support:** National Natural Science Foundation of China (62293551, 61977008), China Postdoctoral Science Foundation (2021TQ0047) Open Research Fund of the State Key Laboratory of Cognitive Neuroscience and Learning (CNLYB2101)

**Title:** In-phase interpersonal coherence correlates with interpersonal attraction

**Authors: *Y. LONG**, S. ZHOU, M. ZHONG, C. LU;
Beijing Normal Univ., BEIJING, China

**Abstract:** Touch is a powerful medium for transmitting emotional and social bonding information. However, it remains unclear whether touch can also stimulate interpersonal attraction, and if so, what are the underlying neural mechanisms? This study aimed to fill this knowledge gap. We measured interpersonal neural synchronization (INS) between opposite-sex strangers using functional near-infrared spectroscopy-based hyperscanning, while pairs of participants either touched or gazed at each other. We found that touch induced higher interpersonal attraction and INS compared to gaze. Importantly, analysis of the phase lag of INS showed that synchronized neural activity between brains (in-phase INS) was associated with interpersonal attraction, while negatively correlated neural activity between brains (out-of-phase INS) showed no such correlation. Furthermore, we identified gender-specific effects in the touch and gaze conditions. In the touch condition, the phase lag of in-phase INS led by men was associated with interpersonal attraction, while in the gaze condition, the phase lag of in-phase INS led by women correlated with interpersonal attraction. This research sheds light on the neural underpinnings of touch in inducing interpersonal attraction, with potential implications for understanding social bonding processes. Additionally, our findings expanded the in-phase and out-of-phase connections from the single-brain to the multi-brain level.

**Disclosures: Y. Long:** None. **S. Zhou:** None. **M. Zhong:** None. **C. Lu:** None.

**Poster**

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**Topic:** G.03. Motivation

**Support:** U01MH122849
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K99HG012229
CZF2019-002443
CZF2018-183446

**Title:** Generation of spatial landscape of gene expression in the human locus coeruleus using spatially resolved transcriptomics and single nucleus RNA-sequencing

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**Abstract:** The locus coeruleus (LC) is a brainstem pontine nucleus that is the primary site for norepinephrine (NE) production in the human brain. The LC-NE system plays prominent roles in several higher order cognitive functions. Furthermore, degeneration and early cell loss of LC-NE neurons is a hallmark of neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. We first confirmed inclusion of the LC in dissected tissue samples from postmortem human pons using single molecule fluorescent in situ hybridization (smFISH). We then generated a spatial map of gene expression in human LC (n=5 neurotypical donors; n=2-4 sections/donor) using the 10x Genomics Visium spatial transcriptomics platform, and performed 10x Genomics single nucleus RNA-sequencing (snRNA-seq) on a subset (n=3) of the same donors to define molecular profiles for LC cell types. We defined spatial gene expression signatures across the LC core and surrounding regions, followed by characterization of molecular profiles for cell types in this region at single nucleus resolution. These analyses revealed expression of cholinergic marker genes within LC-NE neurons, which we confirmed with smFISH. Comparison of this data with published molecular profiles in rodent LC revealed partial conservation of cell types and gene expression patterns across species. In conclusion, we characterized the gene expression landscape of the human LC at spatial and single nucleus resolution, and provided an interactive web resource to explore the data.

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**Poster**

**PSTR041. Motivation: Higher Cognitive Processing**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR041.15/JJ23

**Topic:** G.03. Motivation

**Support:** Duke Institute of Brain Sciences Germinator Award
Charles Lafitte Foundation

**Title:** Whole-brain networks support activation of the ventral tegmental area during motivational thinking with real-time fMRI neurofeedback

**Authors: *R. N. WRIGHT**[1], S. HAKIMI[2], L. YOST[3], J. MACINNES[2], K. C. DICKERSON[2], K. S. LABAR[2], R. ADCOCK[4];
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**Abstract:** People often attempt to motivate themselves using specific thoughts and imagery, with mixed effectiveness. Real-time fMRI neurofeedback training can be a powerful tool to train individuals to link specific mental processes with brain activity. We have previously demonstrated that individuals can learn to upregulate and sustain BOLD activation in the ventral tegmental area during neurofeedback using self-relevant motivational thoughts and imagery. The present study aimed to replicate these findings in a larger sample and extend these findings by examining whole-brain activity during neurofeedback (compared to partial-volume data in the original study). In our current study (n=33), participants were instructed to motivate themselves while increasing a thermometer display of real-time VTA fMRI signal (activate trials) or to count backwards (count trials). To examine transferability, participants completed test trials without neurofeedback before and after training. Whole-brain and ROI analyses replicated the main finding that individuals can learn to increase VTA activity during real-time neurofeedback. Whole-brain analyses revealed significant activation in regions involved in episodic simulation (inferior parietal lobule, dorsolateral prefrontal cortex, inferior parietal lobule, precuneus), reward (midbrain), emotional memory and learning (hippocampus, striatum, amygdala), and visual processing. Targeted ROI analyses also showed significant activation in the nucleus accumbens during neurofeedback training. Examinations of post > pre-training change in activation during motivational enhancement (without neurofeedback) revealed reduced recruitment of the dorsomedial prefrontal cortex and greater recruitment of the cingulate cortex. Collectively, these findings indicate that neurofeedback training can successfully increase VTA activity and reorganize prefrontal engagement during self-motivation.

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**Poster**

**PSTR041. Motivation: Higher Cognitive Processing**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR041.16/JJ24

**Topic:** G.03. Motivation

**Support:** NIH Grant U01MH122849
NIH Grant R01MH123183
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LIBD Funding

**Title:** Benchmarking spot-level deconvolution methods in the human dorsolateral prefrontal cortex using Visium Spatial Proteogenomics

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**Abstract:** Visium (10x Genomics) measures spatial gene expression in ~5000 individual spots, each containing a mixture of cell types. Coupled with immunofluorescence (IF) for cell type markers, Visium Spatial Proteogenomics (Visium-SPG, formerly Visium-IF) allows for simultaneously measuring gene expression while quantifying the number of immunolabeled cell types per spot. Several computational approaches, including SPOTlight, Tangram, and cell2location, have been developed to perform cell type deconvolution of Visium spots. Here we benchmarked these software methods in post-mortem human dorsolateral prefrontal cortex (DLPFC) using Visium-SPG IF antibodies for 4 broad cell types. Tissue sections from 4 adult neurotypical control donors were collected on Visium arrays and immunolabeled for GFAP, NeuN, OLIG2, and TMEM119 to identify astrocytes, neurons, oligodendrocytes, and microglia, respectively. Tissue was counterstained with DAPI to label individual nuclei. Multi-channel fluorescent images were acquired using spectral imaging, and nuclear segmentation of DAPI signals was performed using cellpose. An expert manually classified 342 cells across different Visium spots using Samui Browser, and a decision-tree classifier was trained (88% accuracy) to classify cells on the remaining spots and IF samples. Following imaging, complementary Visium RNA-sequencing libraries were prepared and sequenced. Leveraging paired single nucleus RNA-sequencing DLPFC data, Tangram, cell2location, and SPOTlight softwares were used to map individual cells, with their corresponding cell-type annotation, onto particular spots measured in the Visium-SPG gene expression data. Software-estimated and image-derived counts were compared using correlation and root mean squared error (RMSE). In addition, cell compositions were treated as probabilities, and two composition estimates were compared with measures such as Kullback-Leibler divergence. Depending on the metric used, Tangram or cell2location

performed the best, suggesting that either tool is appropriate for spot deconvolution and selection can be guided by the downstream use case. In summary, we provide a benchmark Visium-SPG dataset and analysis framework to evaluate emerging spot deconvolution algorithms that seek to add cellular resolution to Visium spatial gene expression data. The spot deconvolution results can be interactively explored at http://research.libd.org/spatialDLPFC/.

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**Poster**

**PSTR041. Motivation: Higher Cognitive Processing**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR041.17/JJ25

**Topic:** G.03. Motivation

**Support:** NIH R01MH105592
Lieber Institute for Brain Development Internal Funding

**Title:** Molecular profiling of lateral septum cell types in the human brain

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**Abstract:** The lateral septum (LS) is a subcortical brain region along the medial boundaries of the lateral ventricle. It is involved in many social processes including aggression, sexual behavior, social novelty recognition, and maternal care. These behaviors are frequently altered in neurodevelopmental disorders such as autism and schizophrenia. Our laboratory also recently demonstrated that TrkB-expressing neurons in the LS play an important role in social novelty recognition in mice (Rodriguez et al., 2022). Despite its involvement in a number of critical brain functions, the LS lacks comprehensive molecular characterizations of its cell types. This is particularly true in the human brain where the LS is challenging to isolate anatomically. As such, molecular profiles of human LS cell types have not been available for cross-species analyses with existing rodent data. To address this gap, we generated molecular data from LS tissue blocks dissected from fresh-frozen postmortem human brain slabs (n=3 donors, without documented history of neuropsychiatric illness). The presence and location of LS on each tissue block was confirmed by probing for markers of the LS (*TRPC4*) and surrounding brain areas including the fornix (*MBP*), striatum (*PPP1R1B*), and medial septum *(ELAV2)* using RNAScope

multiplex single-molecule fluorescence *in situ* hybridization (smFISH). Based on this data, we scored each tissue block to enrich for the LS, and then generated single-nucleus RNA sequencing (snRNA-seq) data using the 10x Genomics 3' Gene Expression Chromium platform. We compared this data to our previously generated snRNA-seq data from rodent LS tissue to identify divergence and convergence in gene expression across LS cell types in humans and rodents. These cross-species analyses will further our understanding of the molecular signatures within different LS cell types that can be used to study behaviors modulated by the LS.

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**Poster**

**PSTR041. Motivation: Higher Cognitive Processing**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR041.18/KK1

**Topic:** G.03. Motivation

**Support:** 1R01DA55823

**Title:** Molecular mapping of the human habenula using single cell and spatial transcriptomics

**Authors: *K. D. MONTGOMERY**, B. AJANAKU, E. D. NELSON, H. R. DIVECHA, E. YALCINBAS, R. GARCIA-FLORES, J. WU, J. M. STOLZ, S. KWON, T. M. HYDE, L. A. HUUKI-MYERS, L. COLLADO-TORRES, K. R. MAYNARD;
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**Abstract:** The habenula (Hb) is an epithalamic brain region that plays a critical role in cognition and reward. Dysfunction of the Hb has been associated with both neuropsychiatric and substance use disorders. The Hb is organized into two main regions, the medial habenula (MHb) and the lateral habenula (LHb), which are functionally and cellularly distinct. Due to its small size, few studies have investigated the molecular profile of the human Hb and little is known about the transcriptomic signatures of LHb and MHb cell types in the human brain. Here we sought to generate a molecular map of the human Hb at single cell and spatial resolution using single nucleus RNA-sequencing (snRNA-seq) combined with single molecule fluorescent in situ hybridization (smFISH). To locate the Hb for molecular studies, we conducted smFISH for established Hb marker genes to identify LHb and MHb divisions as well as surrounding white matter tracts. Using the 10x Genomics 3' Gene Expression platform, we performed snRNA-seq on postmortem human Hb from 7 neurotypical adult donors. We identified seven distinct LHb populations and three distinct MHb populations. We defined unique marker genes for these neuronal populations and validated a subset of them using smFISH with RNAscope technology. Finally, we performed cross-species analyses and evaluated the conservation of LHb and MHb subpopulations between the rodent and human brain. In summary, we present the first single cell

molecular atlas of the human Hb and provide an interactive web resource for the scientific community to explore the data.

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**Poster**

**PSTR041. Motivation: Higher Cognitive Processing**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR041.19/KK2

**Topic:** G.03. Motivation

**Support:** NIH Grant R01MH105592
NIH Grant R01DA053581

**Title:** Molecular profiling with spatial resolution of the basolateral complex of the human amygdala

**Authors: *M. R. VALENTINE**[1], M. S. TOTTY[1], S. V. BACH[1], M. TIPPANI[1], S. C. PAGE[1], T. M. HYDE[1,2,3], S. C. HICKS[5,6], K. MARTINOWICH[1,3,4,7];
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**Abstract:** The amygdala is a complex brain structure critical for emotional learning and memory. In humans, aberrant activity in the amygdala is implicated in stress-related disorders including depression, anxiety, and post-traumatic stress disorder. Despite prominent importance in behavior and disease, molecular characterizations of the amygdala with spatial and cellular resolution are lacking, particularly in the human brain. Here, we molecularly characterized the major input region of the human amygdala, the basolateral complex (BLA), using single nucleus RNA-sequencing (snRNA-seq) and spatially-resolved transcriptomics (SRT). Blocks containing the amygdala complex were dissected from fresh-frozen postmortem human tissue slabs (n=5 neurotypical donors). The blocks underwent quality control to ensure inclusion and identify boundaries of the BLA using choline acetyltransferase staining and single-molecule fluorescent *in situ* hybridization (smFISH) for marker genes of key amygdala cell populations, including neurons (*SLC17A7, TAC1, NTS, PDYN, SST,* and *PVALB*) and oligodendrocytes (*MBP*). Histological staining and smFISH were used to guide scoring of the tissue block to isolate and collect the BLA. We then used the 10x Genomics 3' Gene Expression Chromium platform on NeuN+ sorted nuclei for snRNA-seq (n=5) and the 10x Genomics Visium Spatial Gene

Expression platform for SRT (n=1). Hierarchical clustering of single nuclei revealed a wide variety of excitatory (*SLC17A7+)* and inhibitory (*GAD2+*) neuronal cell types, including inhibitory clusters with high expression of well-known marker genes for intercalated nuclei. Spatially-informed, unsupervised clustering methods revealed spatial domains that accurately corresponded to BLA subregions, such as the basal and lateral nuclei, as well as islands of intercalated cells. Finally, differential expression analysis of spatial domains revealed novel marker genes for identifying and distinguishing the basal and lateral subnuclei of the BLA. These data are an important resource for better understanding the molecular composition of the human basolateral amygdala, and provide guidance for future, large-scale single cell and spatially-resolved transcriptomic studies in the human amygdala.

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**Poster**

**PSTR042. Modulation of Positive and Negative Emotional States: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR042.01/KK3

**Topic:** G.04. Emotion

**Title:** Cortical Functionality DURING THE READING OF EROTIC OR AGRESIVE-EROTIC TEXT in young women.

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**Abstract:** Sexual arousal (SA) is a determining physiological state for an individual's optimal sexual response. Among the different stimuli used to generate an AS state at the experimental level is erotic texts. Erotic text often includes aggressive content that has not been evaluated in relation to SA. The aim of this work was to compare cortical functionality by recording electroencephalographic activity (EEG) in young women when reading a sexually explicit text (SET) and a sexually explicit text with aggression (SETA). Twenty-seven healthy women between 20 and 30 years old participated. The EEG activity of frontal, temporal and parietal areas was recorded during the reading of both texts. Participants rated the SET as pleasant compared to the SETA. Both texts were classified as generators of general activation and sexual activation. During the reading of the SETA, a greater absolute power (AP) of the alpha1, alpha2 and beta 1 bands was observed in frontal areas, of theta, alpha1, alpha2 and beta1 in the left parietal, as well as of alpha1, alpha2, beta1 and gamma in right parietal with respect to the SET. Regarding the degree of EEG coupling, during the SETA a greater interhemispheric correlation between frontals (F3 and F4) in delta, and alpha1 and a greater intrahemispheric correlation between frontal-temporal left in alpha2 and beta 1 was observed. These data show that cortical functionality during a state of sexual activation in women varies depending on the type of

content and context of the erotic reading. This cortical EEG changes could be associated to mechanisms that underlying the processing and incentive value assignment of stimuli with sexual and aggressive connotations in young women.

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**Poster**

**PSTR042. Modulation of Positive and Negative Emotional States: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR042.02/KK4

**Topic:** G.04. Emotion

**Support:** PRODEP Grant TCLL-511-6/2020-8632

**Title:** Impact of cognitive distortions on perceived stress, anxiety, and depression in the mexican population

**Authors: *T. CIBRIAN-LLANDERAL**[1], M. PEREZ-HERNANDEZ[1], R. CASTILLO-LOPEZ[2], J. FERNANDEZ-RUIZ[4,1], S. ZAMORA-LUGO[1,3], R. TRIANA-DEL RIO[5];
[1]Inst. de Neuroetologia, [3]Facultad de Psicología, [2]Univ. Veracruzana, Xalapa, Mexico; [4]Dept. de Fisiología, Univ. Nacional Autónoma de México, CDMX, Mexico; [5]Emotional Brain Inst., New York Univ., New York, NY

**Abstract:** Introduction: Cognitive distortions are automatic and biased thought patterns that can lead to misinterpretations of reality. They are distorted mental processes that affect how we perceive, process, and remember information. When we are under stress, our minds tend to be more vulnerable to these cognitive distortions, which can exacerbate feelings of anxiety, worry, and emotional distress. Objective: To describe and analyze the relationship between cognitive distortions and perceived stress, anxiety, and depression in the Mexican population. Method: A descriptive and correlational study was conducted; the research design was cross-sectional and observational. Mexican participants of legal age were evaluated. The Automatic Thoughts Inventory, Perceived Stress Scale, and Beck's Anxiety and Depression Inventories were used as instruments. The correlational structures of the variables of interest were explored using non-parametric analysis, with a significance level set at 0.05. Results: A total of 809 individuals were collected, 74.8% (n=605) of the participants were women. In the total population, there was 87% with high levels of perceived stress, 33.8% moderate/severe anxiety, and 38% moderate/severe depression. The results indicate that cognitive distortions are related to stress, with the most frequent distortions being: interpretation of thoughts (W = 91616, p-value = 0.001876), catastrophic thinking (W = 80682, p= 0.002), fallacy of control (W = 87278, p = 0.006), emotional reasoning (W = 77052, p= 0.004), global labeling (W = 91683, p = 0.002), guilt (W = 83175, p= 0.019), should statements (W = 90530, p= 0.000), divine reward (W = 48411, p= 0.006088). Cognitive distortions of polarized thinking (W = 81996, p = 0.015),

overgeneralization (W = 90697, p= 0.000), emotional reasoning (W = 74668, p= 0.04056), and fallacy of justice (W= 7107, p=0.00) were related to anxiety, while the relationship between cognitive distortions and depression was found in fallacy of reason (W = 92817, p= 0.000) and divine reward (W = 48450, p= 0.005). Conclusion: we found that the variables of stress, anxiety, and depression are indeed related to different cognitive distortions. It is important to note that stress influences the onset and persistence of cognitive distortions. When we are under a chronic stress burden, our minds may become more prone to adopting distorted thought patterns to process information quickly and efficiently, even if it is inaccurate. To manage stress and associated cognitive distortions, it is beneficial to work on developing healthy coping skills and identifying and challenging cognitive distortions.

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**Poster**

**PSTR042. Modulation of Positive and Negative Emotional States: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR042.03/KK5

**Topic:** G.04. Emotion

**Support:** OU Vice President for Research and Partnerships Big Idea Challenge Grant

**Title:** Neural correlates of acute social rejection, resilience and adverse childhood experiences in rural communities

**Authors: *B. ARLEDGE**[1], E. AUGER[2], J. NORRIS[2], S. BELL[4], C. CHAPPLE[3], L. ETHRIDGE[2];
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**Abstract:** The effects of social rejection and isolation may differ between individuals based on personal factors such as past experiences, social support, and resilience. Rural communities are often at greater risk of negative childhood experiences like abuse and neglect and often lack adequate social support or the resources to overcome these experiences, which may affect the way these communities respond to rejection. However, this relationship has not been explored. We hypothesized that individuals with adverse childhood experiences (ACEs) would have increased sensitivity to social rejection. As part of an interdisciplinary study on rural health, we recruited 42 participants living in rural communities (28 women 18-75 years old) to play a cyberball game used to create feelings of rejection by alternating between including and excluding participants from an online game of catch while undergoing 24 channel EEG. Participants completed the Brief Resilience Scale and the Adverse Childhood Experiences Questionnaire. EEG power spectral density was calculated for canonical frequency bands across

frontal, temporal and posterior brain regions. Relative theta power decreased during the rejection condition across frontal $t(28)=-2.48$, $p=.019$, temporal $t(28)=-2.57$, $p=.015$ and posterior $t(28)=-2.12$, $p=.043$ regions when compared to the inclusion conditions, consistent with previous work. Connectivity analyses found significant interaction between rejection/inclusion and resilience (p's<.05) for delta band connectivity for primarily left posterior 28 connections, with 3 surviving FDR correction. Individuals with higher resilience scores tended to have lower delta connectivity during the rejection condition and individuals with lower scores tended to have lower delta connectivity during the inclusion conditions, suggesting a trend toward low frequency activation in response to social rejection in rural individuals with low resilience. No significant differences were found for ACE count on power or connectivity analyses, potentially due to most individuals showing high ACE counts (58% above threshold of 3 ACEs). These results suggest that although resilience does not directly mediate regional brain processes in response to rejection, it does impact neural communication in response to rejection. The results support the concept that personal factors may interact with environmental impacts to affect neural processing vulnerabilities. The information gained from this study can be used to better understand the common experiences in rural communities and the effects these experiences can have on brain development, processes, and overall functioning.

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**Poster**

**PSTR042. Modulation of Positive and Negative Emotional States: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR042.04/Web Only

**Topic:** G.04. Emotion

**Title:** Emotional distress and coping of hospitalized patients

**Authors: K. A. ZAMACONA RUIZ**[1], H. D. MOLINA BELMAN[1], N. V. VEGA-CABRERA[1], *M. FERNANDEZ-MOYA[2], O. A. JARAMILLO-MORALES[1];
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**Abstract:** The prolonged hospital stay of patients can cause discomfort in the emotional state and the way of coping with their health status. The objective of this study was to determine the degree of emotional discomfort and coping of patients hospitalized for a prolonged period at the General Hospital of Irapuato. The Emotional Discomfort Detection questionnaire was applied to a sample of 28 patients from the internal medicine, traumatology, and surgery services of the General Hospital of Irapuato. It was obtained that patients hospitalized for a long period identify at least one issue that worries them, and that significantly affects their state of mind and the way they cope with the current situation they are going through. These results suggest that prolonged hospitalization negatively affects emotional state and coping with the disease.

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**Poster**

**PSTR042. Modulation of Positive and Negative Emotional States: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR042.05/KK6

**Topic:** G.04. Emotion

**Support:** DFG Grant Project-ID 422744262 TRR289

**Title:** Induced expectation of mood improvement activates resource-dependent downregulation of negative inputs

**Authors: *S. BRASSEN**, J. RAUH;
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**Abstract:** Introduction and Methods: Recent reports indicate that placebos achieve around 80% of benefits of antidepressants. This highlights the urgency to minimize placebo responses in clinical trials, but also to understand the mechanisms and predictors of expectation effects and their utility in clinical practice. Previous research shows strong involvement of prefrontal mediated top-down regulation, suggesting a critical impact of goal-directed attentional control, but this has not yet been systematically studied. Here, we investigated the role of attentional resources and cognitive control in effects of positive expectation on emotional processing. Forty-nine healthy volunteers (30 women, mean age 27 years) participated in a cross-over, randomized and controlled 2-day fMRI study in which expectancy of improvements in mood and emotional processing was induced by an alleged oxytocin nasal spray. In the scanner, participants performed a spatial cueing paradigm (Brassen et al., *Biological Psychiatry*, 2011) that manipulated attentional load on emotional face distractors. Results and Conclusions: Following the induction of positive expectations, participants reported higher mood ratings and showed a reduced distractibility by fearful compared to happy faces, but only when more attentional resources were available to process faces. Task effects were directly related to individuals' general cognitive control ability. Imaging analyses, including effective connectivity analyses, demonstrate modulation by expectation in networks involved in emotion perception and regulation, including the anterior cingulate cortex, precuneus, middle frontal gyrus, and amygdala. Changes in networks involved in the control of visuospatial attention were directly correlated with individual cognitive control ability. Taken together, these findings suggest that expectations can modulate the preference for processing specific emotional information by activating top-down attentional orienting, which is driven by individual control ability and attentional context. These findings are of particular relevance regarding the potential benefits of positive expectations in patients with major depressive disorder, who often demonstrate a negativity bias as well as reduced cognitive control capacity.

**Disclosures:** **S. Brassen:** None. **J. Rauh:** None.

**Poster**

**PSTR042. Modulation of Positive and Negative Emotional States: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR042.06/Web Only

**Topic:** G.04. Emotion

**Support:** Brazilian National Council for Scientific and Technological Development (CNPq) Scholarship

**Title:** Long-term yoga experience predicts a facilitated attentional disengagement away from fearful faces

**Authors: *G. CAMPELO**, A. L. AFONSO, W. DE SOUZA, G. M. CASTILHO;
Dept. of Basic Psychological Processes, Univ. of Brasilia, Brasilia, Brazil

**Abstract:** Yoga-based practices are thought to affect top-down and bottom-up emotional attention, but empirical evidence remains incipient. This pilot study tested whether long-term yoga experience (years of practice divided by age, to avoid age-related confounds) and current weekly hours of practice (postures, breathwork, and meditation time in the past 3 months) predicted less emotional interference in two emotional spatial cueing tasks (ESCTs). ESCTs manipulated exogenous or endogenous orienting (150ms or 900ms SOAs), using fearful and neutral faces of high, low, and broad spatial frequencies. It was hypothesized that greater yoga experience and practice would delay attentional engagement, especially to low-spatial frequency fearful faces, under exogenous orienting (as bottom-up emotional attention), and accelerate attentional disengagement, especially from high-spatial frequency fearful faces, under endogenous orienting (as top-down emotional attention). Twenty healthy long-term practitioners participated (sex: 60% female; age: 46.60±12.37; years of experience: 16.40±13.02; years of experience/age: 0.34±0.21; practice hours/week: 7.39±5.60). Participants completed self-report measures, then ESCTs on PsychoPy (264 trials each; 80% cue validity). Yoga experience, but not practice, interacted with ESCTs' RTs, in 2(emotion) x 3(spatial frequency) x 2(validity) GLMs. The exogenous ESCT revealed an emotion*validity*experience effect, $F(1,18)=5.29$, $p=.03$, $n_p^2=.23$, decomposed as attentional engagement (Mean $RT_{neutral\ valid}$ - Mean $RT_{fearful\ valid}$), and disengagement scores (Mean $RT_{fearful\ invalid}$ - Mean $RT_{neutral\ invalid}$). Regression models showed a trend of experience's effect on disengagement, $R^2=.14$, $F=2.91$, $b=.056$ [95%CI: -.013, .125], $SE=.033$, $t(18)=-1.71$, $p=.10$, but not on engagement, $p=.62$. The endogenous ESCT revealed an emotion*validity*spatial frequency*experience interaction, $F(2,34)=6.50$, $p=.004$, $n_p^2=.28$, decomposed as engagement and disengagement scores for each spatial frequency. GLMs showed no effects for engagement, $ps>.05$, but a spatial frequency*experience interaction for disengagement, $F(2,34)=5.31$, $p=.01$, $n_p^2=.24$. As experience increased, broad cues elicited faster disengagement away from fearful cues, $b=-.119$ [95% CI: -.226, -.011], $SE=.051$, $t(17)=-2.33$, $p=.03$, $n_p^2=.24$, but high/low cues did not. Thus, long-term yoga experience predicted a

facilitated attentional disengagement away from fearful faces, more strongly under endogenous orienting, which suggests its primary influence on top-down processes of emotional attention. Specific spatial frequency hypotheses were not confirmed.

**Disclosures:** **G. Campelo:** None. **A.L. Afonso:** None. **W. De Souza:** None. **G.M. Castilho:** None.

**Poster**

**PSTR042. Modulation of Positive and Negative Emotional States: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR042.07/KK7

**Topic:** C.01. Brain Wellness and Aging

**Support:** The project was supported by The University of Hong Kong May Endowed Professorship in Neuropsychology to T.M.C. Lee.

**Title:** Interplay of neural dynamics and depressive symptom severity with sad mood state on attention bias to emotional stimuli

**Authors: *S. T.S.T. MABEL-KENZIE**[1,2], N. M. L. WONG[1,2,3], T. M. C. LEE[1,2];
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**Abstract:** Mood states can affect our attention processing of emotional stimuli. Emotional attention can also be altered in affective disorders, commonly observed as mood-congruent attention bias but little is known about whether neural dynamics play a role in this relationship. This study utilised resting-state fMRI to examine how brain global synchrony and metastability, and depressive severity modulate the effects of mood induction on attention to emotional stimuli. Forty-six healthy adults (19 males; age: *M*=30 years, *SD*=11.3 years) were randomly allocated to either sad or control mood induction where they listened to a 10-minute sad or neutral music excerpt. Participants' attention to emotional words was then measured by the Emotional Stroop task - they had to identify the colour of target word stimuli (positive, negative, neutral) and their reaction time was recorded. Before mood induction, global synchrony and metastability were measured using resting-state fMRI. We first evaluated the effects of mood induction and corresponding mood change on participants' Positive vs. Neutral, Negative vs. Neutral, and Negative vs. Positive interferences. We then investigated whether global synchrony and/or metastability of BOLD signals in ROIs across whole brain and depressive severity modulated the effects of mood induction. Regression and SEM analyses controlling for age and gender were conducted at 5000 bootstrapping. Sad mood induction resulted in sadder mood ($F$=6.90, $p$=0.012), such that mood change mediated the effects of mood induction on the difference in attention to negative and positive stimuli (i.e., Negative vs. Positive interference) (*effect*=0.04, 95% CI [0.003 0.087]). Global synchrony was also associated with mood change post-sad-

induction ($\rho$=-0.55, $p$=0.005) and moderated the indirect effect of mood change on the relationship between mood induction and Negative vs. Positive interference (*effect*=0.39, 95% CI [0.012 1.102]). Depressive severity was not related to global synchrony but was directly related to mood change post-induction ($\rho$=-0.31, $p$=0.035). Introducing the latter association in the SEM model revealed that specific effects of depressive somatic symptoms on mood change added to the significant moderated mediation on Negative vs. Positive interference ($effect_{synchrony-induction}$=0.39, 95% CI [0.055 0.927]; $effect_{somatic}$=0.01, 95% CI [0.0002 0.0214]). Together, individuals with higher neural synchrony (usually relating to lingering in a state) and more depressive somatic symptoms experienced stronger sad mood after sad mood induction and hence, attended longer to (or were more interfered by) mood-congruent emotional stimuli.

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**Poster**

**PSTR042. Modulation of Positive and Negative Emotional States: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR042.08/KK8

**Topic:** G.04. Emotion

**Title:** The role of the inferior frontal gyrus in the processing of ambiguity in emotions: will emotional ambiguity predict avoidance behavior?

**Authors: S. HONG**[1], Y.-Y. CHEN[1], *T.-H. LEE[1,2];
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**Abstract:** Individuals who lack clarity about the nature of their own emotions (i.e., emotional ambiguity tendency) also struggle to accurately perceive others' emotions. This often leads those individuals with heightened emotional ambiguity tendency to avoid social situations due to difficulties in processing emotional information, particularly because emotions in social situations are often expressed in nuanced and ambiguous ways. Recent studies have highlighted the significance of the inferior frontal gyrus (IFG) in perceiving emotions and its role in detecting subtle changes in emotional context. The current study aims to investigate the interactive effects of an individual's emotional ambiguity tendency and IFG activation on avoidance behavior by focusing on situations of social conflict as they induce more diverse emotions. In particular, we examined whether the IFG activation during the processing of ambiguous emotional expression can predict avoidance behaviors in social conflicts. We have recruited 28 young adults ($M$=21.33±4.04; 50% females) and measured 1) their avoidance behavior tendency in a competition and victim rescue behavioral tasks, 2) IFG activation level as a proxy of the neural index of an emotion processing using fMRI task that measured their perception of facial expressions with morphed faces from angry (AN) to neutral (NE) to happy (HA). Additionally, the Difficulties in Emotion Regulation Scale was administered to capture emotional ambiguity tendencies. The results revealed a significant association between emotional ambiguity tendency and avoidance behavior such that individuals with higher

emotional ambiguity tend to avoid social interactions in general ($r$ = 0.394, $p$ = 0.038), and the trend is stronger in socially ambiguous conflicts ($r$ = 0.455, $p$ = 0.015). Importantly, IFG activation level, especially in response to ambiguous facial expressions (≤15% morphing from NE to either AN or HA), showed a negative correlation with avoidance behavior ($r$ = -0.388, $p$ = 0.041), suggesting that individuals with higher IFG processing for the ambiguous information tend to avoid conflicts less. However, there was no direct link between IFG and the emotional ambiguity tendency ($p$ = 0.574). In conclusion, the findings suggest that the IFG may assist in reducing social avoidance by enhancing sensitivity to emotional cues presented subtly. These results contribute to our understanding of the role of emotional ambiguity and IFG activation in avoidance behavior, particularly in the context of social conflicts.

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**Poster**

**PSTR042. Modulation of Positive and Negative Emotional States: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR042.09/KK9

**Topic:** G.04. Emotion

**Title:** Tracking engagement and disengagement during movie viewing with fMRI and subjective annotations

**Authors:** M. NANNI-ZEPEDA[1], G. RAZ[2], T. HENDLER[3], Y. FAN[4], S. GRIMM[5], M. WALTER[6], M. ESTERMAN[7], ***A. ZUBERER**[1];
[1]Dept. of Psychiatry and Psychotherapy, Univ. clinic Tübingen, Univ. Tübingen, Tübingen, Germany; [2]The Steve Tisch Sch. of Film and Television, Tel Aviv, Israel; [3]Psychology, neuroscience and psychiatry, Tel-Aviv Univ., Tel Aviv-Yafo, Israel; [4]Dept. Psychology and Neurosciences, Leibniz Res. Ctr. for Working Envrn. and Human Factors, Dortmund, Germany; [5]Berlin Inst. of Health, Campus Benjamin Franklin, Charité-Universitätsmedizin Berlin, Berlin, Germany; [6]Dept. of Psychiatry and Psychotherapy, Univ. Hosp. Jena, Jena, Germany; [7]Psychiatry, Boston Univ., Boston, MA

**Abstract:** Introduction: Movie paradigms have gained increasing popularity due to their higher ecological validity as compared to traditional repeated stimulus-response paradigms. Movies provide a temporally evolving narrative, wherein individuals can engage, disengage from and re-engage in their own time and pace. However, it has been a challenge to track this rich emotional experience and identify its neural underpinnings. We assessed the potential of using subjective annotations of emotion experiencing to identify discrete moments of engagement and disengagement.
Methods: To this aim, we analyzed independent data sets using two sad and one neutral movie clip together with fMRI and subjective annotations of emotional arousal in healthy individuals (21 Grams and Son's Room (n=21, 28.1, ±6.5 years; Borchardt et al. 2018); Sophie's Choice (n=45, 26.7, ± 4.7 years; Raz et al. 2016). We derived a group manifold from individual time

courses of subjective annotations of emotional arousal using Principal Component Analysis (PCA). We then identified episodes of rises and falls within the fluctuations of the group manifold, which we call here engagement and disengagement, respectively. To assess neural responses underlying momentary engagement and disengagement, we constructed a whole-brain voxel-wise general linear model with either engagement or disengagement episodes as regressors. Specifically, we used a contrast design with Engagement > Disengagement & Engagement < Disengagement. To find movie neural patterns conjunction analysis proposed by (Price and Friston 1997) to find voxels with significant conjoint effects across different data sets using the same contrast, e.g sample1/movie1 (Engagement > Disengagement) ∩ sample2/movie2 (Engagement > Disengagement).
Results: The conjunction analysis revealed common brain patterns across all three movies. Engagement was underpinned by higher activation in visual and attention regions. In contrast disengagement was underpinned by greater activations in default mode regions, i.e. the bilateral middle and superior temporal gyrus and sulcus (MTG/STG and MTS/STS).
Discussion:Together our findings suggest that engagement and disengagement are underpinned by distinct neural response patterns. Engagement drew on brain regions supporting attention shifts towards affective stimuli, whereas disengagement involved brain regions supporting self-referenced processing, possibly in the context of emotion regulation (Mohanty and Sussman 2013).
Conclusion: Fluctuations in subjective markers of arousal draw on common brain patterns during movie viewing. Further research is needed to validate our results.

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**Poster**

**PSTR042. Modulation of Positive and Negative Emotional States: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR042.10/KK10

**Topic:** G.04. Emotion

**Support:** NSF Grant 330698

**Title:** Prediction accuracy of enjoyment is biased towards positive over negative conversations.

**Authors: *I. LEIVA**[1], S. REISMAN[2], R. GAMBOA[1], C. HELION[1], V. MURTY[1], J. JARCHO[1];
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**Abstract:** When we converse with someone for the first time, we often underestimate how much the person enjoyed the conversation, a phenomenon known as the *liking gap*. However, as conversations tend to fluctuate in various domains, it remains uncertain what features we use to generate an overall evaluation. Here, we evaluated how salient events, valence, and

primacy/recency influence predictive accuracy. To study this, gender-matched participants (N=20 dyads; 95% female) followed a 9-question prompted conversation. Questions were randomly presented and evenly split between positive, neutral, and negatively-valenced topics about the personal opinions and experiences of the participants. Following the conversation, participants rated their own enjoyment and made predictions of their partner's enjoyment both for the overall conversation and individual prompts. We found that participants significantly underestimated how much their partner enjoyed the entire conversation ($M$ = -0.83; SD = 0.98; $p < 0.001$). Using a composite score of these actual and predicted ratings, we ran a lasso regression to identify what features of the individual prompts most strongly influenced the overall assessment. We found that the order in which a question was presented (i.e., primacy and recency effects) did not influence overall judgments. However, we found that positive questions contributed to the overall prediction accuracy (M = 0.45; SD = 0.16; $p < 0.01$) more than negative questions (M = 0.19; SD = 0.13). Additional analyses include exploring how linguistic features (e.g., vocal tone, individual and overall valence) of responses influence prediction accuracy, as well as identifying the neural correlates of these different linguistic features via an ongoing fMRI experiment that uses the conversations as stimuli.

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**Poster**

**PSTR042. Modulation of Positive and Negative Emotional States: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR042.11/KK12

**Topic:** G.04. Emotion

**Support:** Sustainable Human Centric Next Generation Manufacturing

**Title:** Development of Emotion Estimator for Dynamic States Using Electroencephalogram and Galvanic Skin Response

**Authors: *A. NARIKAWA**[1], W. WEN[1,2], H. HAMADA[1], A. CHANG[1,2], Y. HONDA[1], S. KANDA[1], H. MIZOGUCHI[3], E. KAKEHASHI[1], M. NISHIO[4], K. MAKINO[5], A. YAMASHITA[1], H. ASAMA[1];
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**Abstract:** For designing production systems, evaluation of mental states in dynamic situations is important. Although there are many studies that considered emotion estimation using questionnaire or physiological signals, few studies conducted experiments in dynamic situations and no method for evaluation of mental states during work involving motion has been

established, yet. Therefore, whether it is possible to estimate mental states during dynamic work, based on physiological signals is not cleared. In this study, we developed emotion estimator for dynamic states using physiological signals. Specifically, our aim is to identify the psychological states during tasks involving movement using physiological measures. In the experiment, we conducted a task simulating order picking, where participants had to retrieve parts from boxes within a time limit and place them in a cart. Seven healthy participants were included (two males and five females; mean age = 27.3 ± 6.8 years). The experiment manipulated two factors: task difficulty (easy vs. difficult) and social-comparative feedback (negative vs. positive). During the experiment, questionnaire about three items (mental stress, a sense of achievement, and motivation) and electroencephalogram (EEG) and galvanic skin response (GSR) were measured. We used k-nearest neighbors (k-NN) machine learning for development of emotion estimator. As input data, we extracted wide frequency bands (θ: 4-8 Hz, α1: 8-10 Hz, α2: 10-13 Hz, α: 8-13 Hz, β1: 13-22 Hz, β2: 22-30, β: 13-30 Hz, and γ1: 30-47 Hz) from EEG and mean and maximum value of GSR. Then, we used independent variables of the experiment and subjective ratings through questionnaires as the ground truth labels. Across all the participants, we achieved high accuracy in classification of difficulty levels and mental stress levels: 87.9% in classifying difficulty levels and 96.5% in classifying mental stress levels on average across all the participants. This suggests that the experiment successfully influenced physiological signals. EEG and GSR have been widely used as indicators of autonomic nervous system activity and are likely to reflect difficulty and mental stress, leading to high accuracy.

**Disclosures:** **A. Narikawa:** None. **W. Wen:** None. **H. Hamada:** None. **A. Chang:** None. **Y. Honda:** None. **S. Kanda:** None. **H. Mizoguchi:** None. **E. Kakehashi:** None. **M. Nishio:** None. **K. Makino:** None. **A. Yamashita:** None. **H. Asama:** None.

**Poster**

**PSTR042. Modulation of Positive and Negative Emotional States: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR042.12/KK13

**Topic:** G.04. Emotion

**Support:** NIH R01DA048096
NIH R01MH121099
NIH R01MH124115
NCTIC (WFUSOM CTSI)

**Title:** Valence Partitioned Reinforcement Learning Models Classify and Predict Mechanistic Differences in the Behavior and Emotional Dynamics of Patients with Treatment-resistant Depression

**Authors: *R. E. JONES**[1,2,3], L. P. SANDS[5], J. D. TRATTNER[2], A. JIANG[2], P. V. GLIGOROVIC[6,7], R. RAMOS[6], H. E. DOUGLAS[6], K. T. KISHIDA[2,3,4];
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Grad. Program, [4]Neurosurg., Wake Forest Univ. Sch. of Med., Winston-Salem, NC; [5]Fralin Biomed. Res. Inst., Virginia Tech. Carilion Sch. of Med., Blacksburg, VA; [6]Psychiatry and Behavioral Med., [7]Anesthesiol., Atrium Hlth. Wake Forest Baptist, Winston-Salem, NC

**Abstract:** Treatment-resistant depression affects one-third of the 300 million people with depression worldwide. Electroconvulsive therapy (ECT) is a common treatment for these individuals that induces a generalized seizure impacting multiple networks in the brain, including those linked to emotion regulation, reward processing, and motivation. Mechanisms involved in processing rewarding and punishing experiences are clearly impacted in depression, yet it is unclear exactly how valence-specific learning and affective processes vary in this disease state or are affected by ECT. We hypothesized that: i) computational depictions of learning and affective processes can characterize differences in behavior and brain processes underlying treatment-resistant depression and ii) there are changes in how learning signals affect emotional states in patients with treatment-resistant depression. To test these hypotheses, we recruited patients consented to start ECT (pre-ECT: N=28) for treatment-resistant depression, as well as participants with or without a diagnosis of depression (non-ECT depression, N=40; no depression controls, N = 41). Participants completed a monetarily incentivized probabilistic reward and punishment learning task while undergoing functional magnetic resonance imaging (fMRI). We also administered the Hamilton Depression Rating Scale to all participants to confirm diagnosis status. Computational models fit to i) choice behavior and ii) self-reported subjective feelings during 1/3 of all trials' outcomes revealed significant differences in how patients with treatment-resistant depression i) learned and changed their behavior to positive and negative feedback and ii) reacted emotionally to sequences of rewarding or punishing outcomes as measured by objective learning signals such as valence-partitioned expected values and prediction errors compared to participants with and without depression. Posterior estimates from each of these two models fit for each individual participant using Bayesian methods were subjected to a leave-one-out linear discriminant analysis. We report that model parameters from the second model (i.e., predicting emotional dynamics from objective learning signals) classify each of the three participant groups - pre-ECT, non-ECT depression, and no depression - with perfect accuracy and precision (AUC=1). Analysis of fMRI data is ongoing, with preliminary results suggesting significant differences in valence and salience networks across these three groups. Our results suggest neural mechanisms to target in patients with depression.

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**Poster**

**PSTR042. Modulation of Positive and Negative Emotional States: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR042.13/KK14

**Topic:** G.04. Emotion

**Support:** NIH grant MH125615

**Title:** Processing of Affective Scenes in Convolutional Neural Networks and Human Visual Pathways

**Authors: *Y. CHEN**, M. DING;
Univ. of Florida, Gainesville, FL

**Abstract:** Corresponding Emotional Representations BetweenProcessing of Affective Scenes in Convolutional Neural Networks and Human Visual Pathwaysl Pathways
Yujun Chen[1], Lihan Cui[1], Mingzhou Ding[1], [1]University of Florida
Convolutional neural networks (CNNs) are shown to be good models of the human visual system. In particular, when processing visual object information, tthe earlier layers of CNNs behave similarly to low-level visual areas in the human cortex (e.g., V1), whereas the deeper layers of CNNs behave similarly to high-level visual areas (e.g., inferotemporal cortex). In this study we sought to examine the similarity and difference in CNNs and human visual pathways when processing affective scenes. FMRI data were recorded from human participants viewing pleasant, neutral and unpleasant images from the International Affective Picture System (IAPS). The VGG 16 trained on ImageNet data and DeepGaze were taken to the CNN models of the human visual system. hat is trained on affective images can sufficiently predict human-rated valence. When tested with images occluded by DeepGaze, the CNN performed significantly worse, implying the high-level salience information captured by DeepGaze are emotion related. To establish a CNN and brain correspondence in emotion processing, we propose to examine the emotional representations between CNNs and fMRI response from human brains using representational similarity analysis (RSA). Using the images from the International Affective Picture System (IAPS), we aim to correlate the representational structures from these two modalities (1) by emotion categories of pleasant, neutral, and unpleasant and (2) by emotion category combined with subcategories of objects and scenes. Through the emotion representational structureApplying the representational similarity analysiss, we aim to (1) characterizetrace emotion processing in the early visual cortex, the dorsal visual cortexl pathway, and the ventral visual cortex, pathway (2) characterize emotion processing in the CNN models, (3)by quantifying the proportion of explainable brain RDM variance captured by specificsampled CNN layers, (4) visualize the emotion representations in visual pathways and CNN layers using multi-dimensional scaling (MDS), and (5) decodes emotion representations in visual pathways using emotion representations from features of CNN layers.

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**Poster**

**PSTR042. Modulation of Positive and Negative Emotional States: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR042.14/KK15

**Topic:** G.04. Emotion

**Support:** CIHR Grant MOP-FDN-148418

**Title:** Visual, semantic, and inter-individual factors guiding gaze behavior during implicit processing of dynamic emotional face stimuli

**Authors: *R. YEP**[1], D. BRIEN[1], B. J. WHITE[1], I. PITIGOI[1], B. C. COE[1], L. ITTI[2], D. P. MUNOZ[1];
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**Abstract:** The efficiency with which we can extract information from human faces reflects the importance of face processing for navigating the many social interactions of our day-to-day lives. While most prior face processing research has used static stimuli and highly structured paradigms, recent evidence suggests that dynamic stimuli and unstructured paradigms may elicit more reliable and ecologically valid behavior. Here we describe the use of a novel eye tracking paradigm, the free viewing faces task, to investigate the visual, semantic, and inter-individual factors guiding gaze behavior during implicit emotional face processing. Healthy adults (n=55; 37 female, 18 male; 18-50 years of age) freely viewed 10 min of dynamic video in which the content changed (in the form of a new clip) every 2-4 sec. 60% of the clips were “no face” clips, featuring natural landscapes, animals, building/street scenes, and human activities, and 40% were “face” clips, featuring human faces expressing positive, neutral, and negative emotions. Face clips were independently rated for valence and arousal and annotated frame-by-frame for face regions of interest (ROIs). Numerous metrics were derived from participants’ gaze behavior, recorded at 500 Hz using an Eyelink 1000 Plus, and their associations with low-level clip properties, high-level clip properties, and inter-individual neuropsychological measures investigated. Compared to no face clips, face clips elicited more frequent saccades characterized by smaller amplitudes, smaller eccentricities from screen center, and shorter fixation durations. These differences were evident as early as the first saccade made following a clip change. On a clip-by-clip basis, larger faces were associated with more frequent, large amplitude saccades separated by shorter fixation durations, and an increased gaze probability within face ROIs. For neutral faces, higher arousal scores were associated with increased gaze probability within face ROIs. On an inter-individual basis, gaze probability within face ROIs was positively associated with measures of interpersonal emotion regulation and negatively associated with measures of anxiety and depression. Finally, despite comparable gaze behavior overall, male participants made longer fixation durations on positive and neutral face clips relative to female participants. Together, these findings provide novel insight into the visual, semantic, and inter-individual factors guiding gaze behavior during the implicit processing of dynamic emotional faces. This work has implications for improved understanding of how emotional face processing may be altered in neuropsychiatric disorders.

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**Poster**

**PSTR042. Modulation of Positive and Negative Emotional States: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR042.15/KK16

**Topic:** G.04. Emotion

**Support:** Gallaudet University Priority Research Grant

**Title:** Negative emotions impact attention for learning in young school-aged children

**Authors: *B. E. WHITE**, K. BAILEY, L.-A. PETITTO;
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**Abstract:** Learning requires attention, but the regulation of cognitive and emotional demands on attention is a complex executive skill for young children. We investigated the impact of cognitive load and negative affect on attention in school-aged children across time. Using innovative game-like computerized cognitive tasks, novel proof of concept data were collected and analyzed from 3 typically-developing children at 2 time points (first and second grades). All children were screened for comparable age-appropriate language and nonverbal intelligence and were right-handed, English monolinguals with no history of neurological/learning disorders. Task 1 measured the impact of cognitive load on attention using a dual-task paradigm. The primary task was a congruent Simon attention task, and the secondary task was a word-level speech recognition task presented in quiet and in speech-shaped noise (+10 dB SNR). Task 2 measured the impact of emotional valence (V) and arousal (A) on attention using a facial affect task. Children mirrored line drawings depicting happy (+V, +A), angry (-V, +A), and sad (-V, -A) facial expressions. To measure attention, children pressed a button when they saw a line drawing of a neutral chimpanzee ape face. Both tasks were presented randomly in a block design with practice. We predicted that cognitive load and negative emotions would trade off with executive attentional resources, and regulating this trade off may improve over time. Accuracy and reaction time were analyzed with linear mixed-effects modeling in R. For Task 1, children were less accurate and responded faster when listening in noise compared to quiet. Performance did not improve over time. For Task 2, children responded fastest during happy, slower during angry, and slowest during sad emotional states. Children responded faster over time, but the pattern between emotions remained the same. These findings suggest that early childhood attention is sensitive to changes in emotional states. Listening to speech in noise typical of a busy classroom can increase cognitive load and trade off with attention flexibility, which impacts children across grade levels. Likewise, negative affect trades off with processing speed, even across the maturational development of these emotions. Next, we will test the relationship between these behavioral patterns and physiological measures of cognition (fNIRS brain imaging) and emotion (thermal infrared imaging). These findings provide new insight about optimal learning conditions for young children and across life. The goal of this work is to translate such combined behavioral/neuroscience studies to benefit clinical groups.

**Disclosures: B.E. White:** A. Employment/Salary (full or part-time); Gallaudet University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Gallaudet University. **K. Bailey:** A. Employment/Salary (full or part-time); Gallaudet University. **L. Petitto:** A. Employment/Salary (full or part-time); Gallaudet University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you

are a PI for a drug study, report that research relationship even if those funds come to an institution.; Gallaudet University.

**Poster**

**PSTR042. Modulation of Positive and Negative Emotional States: Human Studies**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR042.16/KK17

**Topic:** G.04. Emotion

**Support:** NIH grant R21AG067024
NIH grant R01AG072893
NIH grant R01CA218501
VA Merit Award CX001301

**Title:** Neural correlates of negative emotional memory in anxiety and interaction with age

**Authors: *S. CHAUDHARY**[1], S. ZHANG[1], Y. CHEN[1], J. C. DOMINGUEZ[3], H. H. CHAO[2], C.-S. R. LI[4];
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**Abstract:** Older relative to young people experience less anxiety; consistent with the 'positivity-effect' in aging, however, the neural processes supporting this age-related difference remain less clear. Negative emotions can enhance as well as impair memory depending on the learned context. Here, we examined how memory of negative emotional images varied with age and whether the underlying neural processes reflect age-related differences in anxiety. Fifty-one healthy adults (age 22 to 80 years, 23 women) participated in clinical assessment with the Spielberg State Trait Anxiety Inventory (STAI) and underwent brain imaging with a memory encoding task where negative and neutral emotional images were displayed pseudo-randomly. Post-scan, participants recognized "new" and "old" images. Sensitivity (true positive rate) and bias (false positive rate) were quantified for individual participants. The results showed that age was negatively correlated with both STAI state score and sensitivity, controlling for bias, in negative emotional memory. However, STAI state score and sensitivity were not significantly correlated. In whole brain regression, STAI state score was correlated with higher activity of the right middle/superior temporal gyri and temporo-parietal junction (MTG/STG/TPJ) for the contrast of "negative correct - incorrect" - "neutral correct - incorrect" trials. Further, MTG/STG/TPJ activity (β) was also negatively correlated with age. Mediation analyses supported a complete mediation model of age -> less anxiety -> less MTG/STG/TPJ β and incomplete mediation of age -> less MTG/STG/TPJ β -> less anxiety. Earlier literature has noted implications of MTG/STG/TPJ in emotion processing, emotion enhancement of memory as well as social cognition. Together, present findings demonstrated age-related changes in negative emotional memory and how age-related reduction in anxiety is reflected in diminished temporal cortical activities during encoding of negative emotional memory.

**Disclosures:** **S. Chaudhary:** None. **S. Zhang:** None. **Y. Chen:** None. **J.C. Dominguez:** None. **H.H. Chao:** None. **C.R. Li:** None.

**Poster**

**PSTR043. Animal Models of Mood Disorders: Neuromodulation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR043.01/KK18

**Topic:** G.05. Mood Disorders

**Support:** MH077681
DA050986

**Title:** Acetylcholine signaling in the medial prefrontal cortex increases learned helplessness behavior in mice

**Authors: *Z. I. ABDULLA**[1], R. B. CROUSE[1], I. M. ETHERINGTON[1], Y. S. MINEUR[1], H. YOUSUF[2], J. J. NA[1], M. R. PICCIOTTO[1];
[1]Yale Sch. of Med., New Haven, CT; [2]Yale Univ., New Haven, CT

**Abstract:** Acetylcholine (ACh) signaling is implicated in the etiology of depression, but is also important for learning, memory, and attention, suggesting that optimal levels are beneficial, while excessive increases are detrimental to affective health. Prolonged ACh signaling during highly stressful events could therefore lead to negative encoding bias, in which stressful experiences are both attended to and encoded more potently, leading to increased depressive symptoms. Therefore, we recorded ACh transients from medial prefrontal cortex (mPFC) during induction of learned helplessness (LH) behavior to evaluate parameters under which cholinergic signaling might alter information processing during stressful events. To this end, $GRAB_{ACh}$ 3.0 was infused into mPFC of male and female mice, and a fiber was implanted above the injection site. In the LH procedure mice undergo two days of 1h trials of inescapable shocks (induction trials) and were tested for active avoidance on Day 3 (30 trials, 0.3 mA). Expectedly,escape latencies were significantly longer in mice following inescapable shock. During induction, mPFC ACh transients rose at each shock initiation and stayed high across presentation, decreasing slowly at termination. Both male and female mice displayed escape deficits, but intensity of ACh signaling across shock presentations correlated positively with escape deficits only in males. We then used a chemogenetic approach to ascertain if modulating cholinergic signaling via excitation or inhibition of ChAT neurons in the mPFC was sufficient to influence LH escape behavior. In males infused with a Gq-DREADD, CNO administration increased escape latencies in active avoidance testing, while Gi-DREADD-mediated inhibition reduced escape latencies, consistent with fiber photometry data. In females however, both Gi- and Gq-DREADD expression led to increased escape latency following CNO administration, suggesting an optimal range of ACh mPFC signaling is required for optimal LH outcomes. To conclude, we identified robust mPFC ACh responses during induction of LH behavior that correlate significantly with escape during active avoidance and identified a potentially important sex

difference, indicating that stress-induced depressive symptoms may be differentially regulated by mPFC ACh signaling in males and females.

**Disclosures: Z.I. Abdulla:** None. **R.B. Crouse:** None. **I.M. Etherington:** None. **Y.S. Mineur:** None. **J.J. Na:** None. **M.R. Picciotto:** None.

**Poster**

**PSTR043. Animal Models of Mood Disorders: Neuromodulation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR043.02/KK19

**Topic:** G.05. Mood Disorders

**Support:** Swiss National Science Foundation

**Title:** Cholinergic modulation of auditory thalamus upon associative fear learning

**Authors:** J. AMORIM FREIRE[1], B. BASKURT[2], J. A. TAYLOR[1], C. M. BENOIT[2], M. HASEGAWA[3], D. A. GANEA[1], M. WEISS[1], Y. LI[5], ***J. GRÜNDEMANN**[4];
[1]Univ. of Basel, Basel, Switzerland; [3]DZNE Bonn, [4]Neural Circuit Computation, [2]DZNE, Bonn, Germany; [5]Peking Univ., Peking Univ., Beijing, China

**Abstract:** Associative learning links predictive sensory stimuli from the environment with their outcomes. The accuracy of this learning will depend on reliable integration of sensory inputs that result in behavioral adaptations to ensure an animal's survival. Several cortical and limbic brain areas have been identified as sites for associative learning. However, the role of thalamic structures that relay sensory information is largely unknown. The medial geniculate body (MGB), or auditory thalamus, is a site of convergence for auditory as well as somatosensory information and is crucial for associative learning (e.g. in fear conditioning). It receives feedforward sensory as well as neuromodulatory inputs. One prominent neuromodulatory cholinergic input to MGB originates in the pedunculopontine tegmental nucleus (PPT). However, the role of brainstem cholinergic inputs to MGB during associative learning remains elusive. Here, we use a combination of deep brain calcium imaging techniques such as fiber photometry and miniaturized microscopes combined with optogenetics to unravel the functional role of cholinergic projections in MGB during associative fear learning in freely moving mice. We found that optogenetic manipulation of cholinergic PPT inputs in MGB during fear acquisition affects learning. Furthermore, we show that cholinergic projections from the brainstem modulate sensory responses of MGB neurons during fear conditioning. This study identifies a role of brainstem cholinergic inputs in multimodal sensory integration during fear conditioning in MGB, which broadens our view on how neuromodulators contribute to associative learning in thalamic areas.

**Disclosures: J. Amorim Freire:** None. **B. Baskurt:** None. **J.A. Taylor:** None. **C.M. Benoit:** None. **M. Hasegawa:** None. **D.A. Ganea:** None. **M. Weiss:** None. **Y. Li:** None. **J. Gründemann:** None.

**Poster**

**PSTR043. Animal Models of Mood Disorders: Neuromodulation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR043.03/KK20

**Topic:** G.05. Mood Disorders

**Support:** NIH Grant MH077681

**Title:** Cholinergic and Noradrenergic Regulation of Basolateral Amygdala Stress Responses

**Authors: *A. R. SOARES**, C. FAI, Y. S. MINEUR, M. R. PICCIOTTO;
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**Abstract:** An important feature common to many stress- and mood-related disorders is the disruption of healthy coping strategies in the face of acute stress, leading to transition towards more maladaptive coping behaviors. Clinical and preclinical research have highlighted acetylcholine (ACh) and norepinephrine (NE) as key mediators of stress reactivity; both neuromodulators converge on the basolateral amygdala (BLA), an important node in stress circuits. Interactions between these two neuromodulatory systems appear to be critical for producing adaptive coping responses tailored to the type of stressor. To investigate the independent and cooperative roles of ACh and NE in coping behavior, and how they change with the controllability of the stressor, we performed fiber photometric recordings of extracellular ACh and NE in the mouse BLA during escapable and inescapable stress. Escapable stress was modeled by the looming shadow test, in which mice were presented with an expanding disc mimicking a descending aerial predator; in this assay, mice exhibit a passive coping response by freezing, or an active coping response by fleeing into a shelter. Inescapable stress was modeled by the tail suspension test, during which mice transition between bouts of struggling (active coping) and immobility (passive coping). Fiber photometric recordings using a GPCR-Activation-Based (GRAB) ACh sensor revealed that BLA ACh levels increased preceding active coping responses, regardless of stress controllability. Using the GRAB NE sensor, fiber photometry showed that NE was elevated during passive coping to escapable stress, but active coping to inescapable stress. Furthermore, these data identified interesting temporal differences in release dynamics: ACh release is more transient and time-locked to behavior, whereas NE release is sustained over longer time periods, suggesting that perhaps quick bursts of ACh drive attention to threats and signal motor responses, while NE integrates information about the nature of escapability of the stressor. Dual-channel recordings to measure levels of both neuromodulators simultaneously will refine understanding of the temporal relationships between these systems, and chemogenetic and optogenetic manipulations of cholinergic and noradrenergic inputs to the BLA will identify causal relationships between release dynamics and behavioral outcomes, providing further insight into the circuits controlling stress responses.

**Disclosures: A.R. Soares:** None. **C. Fai:** None. **Y.S. Mineur:** None. **M.R. Picciotto:** None.

**Poster**

**PSTR043. Animal Models of Mood Disorders: Neuromodulation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR043.04/LL1

**Topic:** G.05. Mood Disorders

**Support:** Jean Phillips Shibley Endowment
Minciencias Fulbright Colombia
T32DA017629

**Title:** Adolescent Vulnerability for Long-Term Psychiatric Disorders: The Role of Acetylcholine, Genetics, Sex, and Stress

**Authors: *T. J. GOULD**[1], C. NOVOA[1], P. GARCIA-TREVIZO[2];
[1]Biobehavioral Hlth., The Pennsylvania State Univ., University Park, PA; [2]The Pennsylvania State Univ., Pennsylvania State Univ., State College, PA

**Abstract:** Adolescence is a period of dynamic change that involves increased risk taking, which may be a necessary part of developing into an independent adult. However, risk taking can also lead to engagement in maladaptive behaviors and challenges. Adolescent exposure to these challenges combined with dramatic neurodevelopmental changes potentially convey increased vulnerability for psychiatric disorders, some of which may manifest later in life. The studies described here employed a mouse model to examine the propensity of adolescent nicotine exposure and stress exposure to produce adult maladaptive phenotypes that model endophenotypes of psychiatric disorders such as addiction and anxiety and the contribution of genetics, sex, and changes in acetylcholinergic function to these endophenotypes. Male and female adolescent mice of mixed genetic backgrounds were exposed nicotine. In addition, other adolescent mice were exposed to social stress. Exposure occurred only during adolescence. In adulthood, anxiety-like behaviors (elevated plus maze and exploration of an open field) along with changes in the cholinergic system were assessed. Adolescent nicotine exposure produced sex-specific changes in adult anxiety-related behavior that was moderated by genetic background. Adolescent nicotine exposure also decreased adult sensitivity to nicotine and had a sex specific effect on nicotine metabolism. Similar to adolescent nicotine exposure, adolescent stress exposure altered adult anxiety-related behavior. These results demonstrate that challenges in adolescence such as nicotine exposure or social stress altered adult responses and mediated changes in adult endophenotypes of psychiatric disorders. These effects were moderated by sex and genotype. Together, these studies speak to the critical role of adolescent development in adult psychiatric health.

**Disclosures: T.J. Gould:** None. **C. Novoa:** None. **P. Garcia-Trevizo:** None.

**Poster**

**PSTR043. Animal Models of Mood Disorders: Neuromodulation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR043.05/LL2

**Topic:** G.05. Mood Disorders

**Support:** NINDS IRTA

**Title:** Type III NRG1 interaction with TrKA signaling in basal forebrain cholinergic neurons regulates mitochondrial motility and axonal maturation.

**Authors: *D. FREEMAN**[1,2], K. HOSPES[2], P. RAJEBHOSALE[3], D. TALMAGE[2], L. ROLE[2]; [1]NIH/NINDS, Washington DC, DC; [2]NINDS, Bethesda, MD; [3]NINDS, NIH/ NINDS, Bethesda, MD

**Abstract:** Type III Neuregulin 1 (NRG1) is a bi-directional transmembrane signaling protein that supports neurodevelopment and has been identified as a candidate gene for schizophrenia in genomic studies. NRG1 regulates the surface expression of cholinergic receptors on hippocampal axons but its effect on cholinergic axons is unknown despite evidence that disruptions in cholinergic signaling cause cognitive distortions related to psychosis. We used spatial transcriptomics in wild-type mice to measure expression of NRG1 across the basal forebrain and observed that medial septum cholinergic neurons have less expression than in the nucleus basalis. We tested whether NRG1 expression is important for cholinergic development using primary cultures of the basal forebrain and measured changes in cellular morphology and axonal branching with respect to NRG1 and its stimulation by Erbb4. Cholinergic projections form highly branched axonal arbors that require a healthy pool of mitochondria at pre-synaptic terminals. Mitochondria are actively transported into terminals and maintain the ability to transition between motile and non-motile states. Changes in motility are driven by local signaling. We tested whether NRG1 signaling during development altered axonal branching via modulation of mitochondrial motility states. We tracked mitochondrial movement in response to NRG1 stimulation using a cholinergic specific mito-GFP tag and observed increases in motility that was dependent on downstream activation of PI3K and different than the pausing behavior observed in hippocampal neurons. We predicted that cholinergic-specific responses to NRG1 signaling were related to the presence of the receptor, TrkA, that is uniquely expressed on cholinergic axons. NGF/TrkA signaling has been shown to increase mitochondrial recruitment to terminals of sensory axons and similarly modulates mitochondrial motility via PI3K. We saw decreases in motility in projections after NGF starvation and interestingly, stimulation of NRG1 in starved cultures had neuron-specific effects that we predict are associated with differences in its expression. We're now characterizing the effect of NRG1 x TrKA interactions on mitochondrial distribution in axons during different timepoints of development and its effect on axonal maturation. These data reveal a novel mechanism for NRG1 regulation TrkA and mitochondrial dynamics in the basal forebrain and provide further evidence for the importance of NRG1 for the survival of cholinergic neurons.

**Disclosures:** **D. Freeman:** None. **K. Hospes:** None. **P. Rajebhosale:** None. **D. Talmage:** None. **L. Role:** None.

**Poster**

**PSTR043. Animal Models of Mood Disorders: Neuromodulation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR043.06/LL3

**Topic:** G.05. Mood Disorders

**Support:** NINDS Intramural Program

**Title:** Ventral pallidal cholinergic input to the basolateral amygdala mediates valence encoding of olfactory stimuli

**Authors: *R. KIM**, M. ANANTH, L. ROLE, D. TALMAGE;
NIH, Natl. Inst. of Neurolog. Disorders & Stroke (NINDS), Bethesda, MD

**Abstract:** The ventral pallidum (VP) is involved in encoding hedonic value of external stimuli. The VP is comprised of a variety of cell types including cholinergic neurons, whose function, until recently, was unclear. We have previously found two distinct subpopulations of VP cholinergic neurons that differentially encode valence: one subpopulation activated in response to a positive valence stimulus (appetitive odor), and a second, non-overlapping subpopulation activated in response to a negative valence stimulus (aversive odor). VP cholinergic neurons primarily project to the basolateral amygdala (BLA), a region also identified as having distinct neuronal subpopulations that encode valence. Whether valence encoding VP cholinergic neurons form functional connections with valence encoding BLA neurons remains unknown. To determine if VP cholinergic neurons work in conjunction with the BLA to encode valence of olfactory stimuli, we first examined changes in BLA activity induced by valence-specific odors. We found that both the appetitive and aversive odor significantly increased cFos activation in the BLA. Furthermore, both odors induced acetylcholine release in the BLA. Next, using in-vivo single-cell calcium imaging, we identified valence encoding neurons in the BLA that were exclusively activated by each odor. In comparison to negative valence BLA neurons that were only activated in response to the aversive odor, a greater percentage of BLA neurons were classified as positive valence neurons (i.e., neurons activated only by the appetitive odor). To investigate the relationship between VP cholinergic neurons and valence encoding BLA neurons, we examined the effects of optogenetic stimulation of VP cholinergic terminals on valence identified BLA neurons. Preliminary results revealed that pairing odor delivery with optogenetic stimulation of VP cholinergic terminals in the BLA changed the ratio of identified positive vs. negative valence BLA neurons. BLA neurons became increasingly responsive to the aversive odor and resulted in corresponding behavioral changes. Although optogenetic stimulation did not alter avoidance to the aversive odor, stimulation of VP cholinergic terminals in the BLA abolished approach to the appetitive odor. Ongoing studies specifically target and manipulate negative vs. positive valence VP cholinergic neurons and map their functional connections with valence encoding BLA neurons.

**Disclosures:** **R. Kim:** None. **M. Ananth:** None. **L. Role:** None. **D. Talmage:** None.

**Poster**

**PSTR043. Animal Models of Mood Disorders: Neuromodulation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR043.07/LL4

**Topic:** G.05. Mood Disorders

**Support:** Villanova Undergraduate Research Fellowship Grant

**Title:** Exploring the impact of brain 5-HT deficiency on exercise-induced alterations in behavior and hippocampal neurogenesis in adult mice

**Authors: *L. ISKANDER**[1], A. WARNER[2], K. ALLEN[2], I. QUATELLA[2], B. SACHS[1]; [2]DEPARTMENT OF PSYCHOLOGICAL AND BRAIN SCIENCES, [1]Villanova Univ., Villanova, PA

**Abstract:** Exercise is known to have beneficial effects on mood and cognition. These effects have been hypothesized to result from increases in adult hippocampal neurogenesis. Serotonin (5-HT)is known to be a critical regulator of adult hippocampal neurogenesis, and mice that completely lack brain 5-HT, tryptophan hydroxylase 2 (Tph2), fail to increase neurogenesis following exercise.However, whether partial loss of Tph2 activity would also prevent exercise-induced neurogenesis and/or the antidepressant-like behavioral effects of exercise is unknown. The current study used Tph2 (R439H) knockin mice (KI), which exhibit 60-80% reductions in brain 5-HT, to determine the effects of low levels of brain 5-HT on behavioral and neurogenic responses to exercise. The behavioral consequences of exercise were evaluated using four common tests of antidepressant-like or anxiolytic behavior: the novelty suppressed feeding (NSF) test, the forced swim test (FST),the novel open field (NOF) test, and the elevated plus maze (EPM). Following behavioral testing, immunohistochemistry was used to quantify cellular proliferation in the dentate gyrus (with antibodies against bromodeoxyuridine (BrdU)) and the number of immature neurons (with antibodies against doublecortin (DCX)).
In females, exercise significantly reduced immobility time in the FST and latency to feed in the NSF test. However, a significant genotype-by-exercise interaction was observed by two-way ANOVA in which these effects were more pronounced in WT mice compared to KI animals.In males, exercise did not lead to an antidepressant-like effect in the FST, but a significant genotype-by-exercise interaction was observed in the NSF, with only WT mice experiencing asignificant reduction in feeding latency. These results suggest that low levels of brain 5-HT are required for some of the antidepressant-like effects of exercise. However, the ability of exercise to promote hippocampal neurogenesis was not impaired in Tph2KI mice relative to WT animals.Rather, Tph2KI females were more sensitive to the neurogenesis promoting effects of exercise than their WT counterparts, despite being less sensitive to several behavioral effects of exercise.This suggests that the magnitude of antidepressant-like effects of exercise is not dependent on the magnitude of the neurogenesis-promoting effects of exercise. These results provide new in sight into the importance of 5-HT and neurogenesis in the antidepressant-like

effects of exercise, and ultimately suggest that exercise may represent a potential alternative to SSRIs for individuals with impaired 5-HT synthesis.

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**Poster**

**PSTR043. Animal Models of Mood Disorders: Neuromodulation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR043.08/LL5

**Topic:** G.05. Mood Disorders

**Support:** TIFR Intramural Grant to VAV

**Title:** Dichotomous role of serotonin during different developmental epochs.

**Authors: *U. GHAI**[1], P. CHACHRA[2], S. FANIBUNDA[3], A. SARKAR[2], K. K.[2], S. MENDON[2], A. BJ[2], V. SINGH[2], U. KOLTHUR[2], V. A. VAIDYA[2];
[1]Tata Inst. of Fundamental Res., Mumbai, India; [2]Dept. of Biol. Sci., Tata Inst. Of Fundamental Res., Mumbai, India; [3]Kasturba Hlth. Society-MRC and Vaidya Lab-TIFR Alliance, Mumbai, India

**Abstract:** Serotonin is known to regulate the development of anxio-depressive behavior. To understand the establishment of these behaviors we focused on two early time windows, namely: Postnatal and Juvenile windows. To modulate levels of serotonin we used a Selective Serotonin Reuptake Inhibitor (SSRI), Fluoxetine. Postnatal Fluoxetine (PNFlx) evoked long-lasting increases in anxio- depressive behavior, whereas Juvenile Fluoxetine (JFlx) elicited persistent decreases in anxio- depressive behavior. To understand the underlying molecular mechanisms that could lead to such differential behavioral effects we investigated the global transcriptome in the medial prefrontal cortex (mPFC) of animals with a history of PNFlx and JFlx. The starkly differing behavioral outcomes were accompanied by differential global transcriptome changes in the mPFC, with minimal overlap in gene regulation. Further analysis highlighted a differential regulation of gene clusters involved with mitochondria, metabolism, synapse, and dendritic development with PNFlx and JFlx. Opposing effects on proteins involved in mitochondrial biogenesis and function were observed, with a decline in PNFlx animals in contrast to the increase following JFlx treatment. In addition, we found opposing effects on the ATP levels and Oxphos efficiency with a significant decline observed with PNFlx in contrast a significant increase was observed with JFlx.Our microarray showed regulation of gene clusters involved in synaptic and dendritic arborizations. We observed a significant downregulation of mTOR pathway components with PNFlx opposing to this a significant increase was observed with JFlx. We observed a significant decrease in the total length and number of apical dendrites with PNFlx contrasting to this we observed a significant increase with JFlx treatment in layer II/III pyramidal neurons of the infralimbic (IL) region of the mpfc.Since PNFlx showed a significant increase in

the anxio- depressive behavior accompanied by a decline in mitochondrial protein levels and OxPhos efficiency. We hypothesized that the decrease in the ATP levels with PNFlx could contribute to the anxiogenic and pro-depressive effects observed with PNFlx. Upon administration of the mitochondrial booster Nicotinamide (NAM) to animals with a history of PNFlx. We observed a significant increase in the levels of ATP and alleviation of the pro-depressive effects observed with PNFlx.Our findings highlight two distinct windows of early life in which SSRI exposure evokes starkly differing effects on behavior, gene regulation, and bioenergetics while establishing a link between bioenergetics and despair-like behavior.

**Disclosures:** **U. Ghai:** None. **P. Chachra:** None. **S. Fanibunda:** F. Consulting Fees (e.g., advisory boards); S.E.F serves as a consultant to Beckley Psytech which is not relevant to the current work. **A. Sarkar:** None. **K. K.:** None. **S. Mendon:** None. **A. Bj:** None. **V. Singh:** None. **U. Kolthur:** None. **V.A. Vaidya:** None.

**Poster**

**PSTR043. Animal Models of Mood Disorders: Neuromodulation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR043.09/LL6

**Topic:** G.05. Mood Disorders

**Title:** Diversity in the neural responses to serotonin (5-HT) agonism in the mouse Piriform cortex

**Authors: J. P. .CHELLIAH**[1], B. GURUNG[1], *S. A. NEALE[2], T. E. SALT[2], J. T. BROWN[1]; [1]Clin. and Biomed. Sci., Exeter Univ., Exeter, United Kingdom; [2]Neurexpert Limited, Newcastle Upon Tyne, United Kingdom

**Abstract:** Neurons in the cortex are heterogeneous in their neurophysiological and neuropharmacological properties and form diverse subsystems that have distinct roles. The piriform cortex plays a key role in olfaction and is known to be a site of epileptogenesis. 5-hydroxytryptamine (5-HT; serotonin) is a key neurotransmitter that is known to modulate neuronal activity in a wide variety of brain centres, including the piriform cortex. Indeed, the piriform cortex receives input from 5-HT-releasing neurons and a sub-population of neurons within the piriform cortex are known to respond to exogenous serotinergic agonist application. However, previous studies have not fully explored the diversity in agonist-induced responses to 5-HT in this brain region. In this study, we used a multielectrode array (MEA) to record spontaneous action potential activity of piriform cortex neurons in brain slices prepared from mice before and after local delivery of 5-HT. Overall, application of high concentrations of 5-HT (100 µM) led to a significant increase in firing rate in certain subpopulations of piriform cortex neurons. However, we uncovered significant diversity in these agonist-evoked responses, including sustained increases, sustained decreases, transient increases and delayed increased. These results indicate that 5-HT can dynamically shape the properties of neural circuits in the

piriform cortex in a complex manner. These findings are potentially important in interpreting the actions of psychoactive drugs that may interact with serotonergic receptors.

**Disclosures:** **J.P. .Chelliah:** None. **B. Gurung:** None. **S.A. Neale:** A. Employment/Salary (full or part-time); Neurexpert Limited. **T.E. Salt:** A. Employment/Salary (full or part-time); Neurexpert Limited. **J.T. Brown:** None.

**Poster**

**PSTR043. Animal Models of Mood Disorders: Neuromodulation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR043.10/LL7

**Topic:** G.05. Mood Disorders

**Support:** Betty Huse, M.D. Charitable Foundation
Summer 2023 SURF Award

**Title:** Exploring the role of steroid hormones in adolescent depression

**Authors: G. B. DREW**[1], T.-C. M. MOU[2], T. D. GOULD[2], *P. GEORGIOU[1];
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**Abstract:** Major depressive disorder affects approximately 13% of adolescents in the United States. While classical antidepressant treatments effectively reduce depressive symptoms in adolescents, low remission rates and potential adverse effects, such as suicide-related thoughts, highlight the need for the development of novel pharmacotherapies for the treatment of adolescent depression. During adolescence, there is a surge in steroid gonadal hormones that impact behavior and brain functions in both humans and mice. Stress in the form of victimization and bullying is prevalent among adolescents and, when combined with increased gonadal hormones, is associated with adolescent depression and suicidality. We hypothesize that the increased risk of depression in adolescents is due to the combined effects of increased stress and heightened production of gonadal hormones in both sexes. Therefore, we propose that targeting gonadal steroid hormone systems could serve as an intervention for adolescent depression and suicidality. To test this hypothesis, we subjected adolescent male and female mice to acute foot-shock stress and assessed the development of anhedonia, social preference deficits, and anxiety-like behavior using the sucrose preference test, social interaction test, and light/dark box test, respectively. We found that stressed adolescent mice displayed social interaction deficits, but no changes were observed in anxiety behavior or anhedonia. To investigate the role of gonadal hormone systems in these effects, we conducted RNAseq analysis on the prefrontal cortex of depressed patients, comparing adults and adolescents. Intriguingly, the gene ontology analysis for biological processes revealed significant downregulation in cholesterol metabolic and biosynthetic processes in adolescent patients compared to adult patients. Cholesterol serves as the precursor for most steroid gonadal hormones. Additionally, pathway enrichment analysis

indicated downregulation in steroid biosynthesis. These findings suggest that dysregulation in steroid gonadal hormone synthesis during adolescence may elevate the risk of developing depression. Consequently, targeting these systems could represent a novel strategy for treating adolescent depression.

**Disclosures: G.B. Drew:** None. **T.M. Mou:** None. **T.D. Gould:** None. **P. Georgiou:** None.

**Poster**

**PSTR043. Animal Models of Mood Disorders: Neuromodulation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR043.11/LL8

**Topic:** G.05. Mood Disorders

**Support:** Simons Foundation Senior Fellowship (Project 328183)
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**Title:** Oxytocin signaling in astrocytes prevents depressive-like behaviors induced by social isolation in male mice

**Authors: *M. SELLES**[1], R. C. FROEMKE[2], M. V. CHAO[3];
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**Abstract:** Social deprivation can have devastating consequences in many species including mice and humans. However, the underlying mechanisms that link social deprivation to differential behavioral consequences are not well understood. Oxytocin is a neuropeptide that is a key player in the regulation of social behaviors. Here we focus on the effects of long-term adult social isolation on the oxytocinergic system and its consequences on the development of depressive-like behaviors in male mice. We found that social deprivation from the age of two to three months reduced the expression of oxytocin in male mice compared to controls (evaluated by qPCR, N=14-15 mice per group, $p<0.05$).Based upon this observation, we delivered intranasal oxytocin to increase levels of this peptide during prolonged social isolation. We treated the mice three times a week for the four week-long isolation period with a dose of 8 ng of oxytocin or PBS as control. We found that intranasal oxytocin prevented the depressive-like behaviors induced by social isolation (evaluated in the Forced Swim Test, N= 13-15 mice per group; grouped PBS vs. isolated PBS $p<0.05$, isolated PBS vs. isolated oxytocin $p<0.05$). To investigate the cell type responsible for these effects, we focused on astrocytes which are capable of expressing oxytocin receptors to modulate mood behaviors. We hypothesized that oxytocin signaling in astrocytes might be responsible for the protective effect of oxytocin against social isolation induced depressive-like behaviors. To test this hypothesis, we generated an inducible

oxytocin receptor conditional mouse specifically in astrocytes and tested the effect of exogenous oxytocin to alleviate depressive-like behaviors induced by social isolation. We found that isolated male KO mice were no longer protected by oxytocin (N= 6 mice per group; isolated KO PBS vs. isolated KO oxytocin p=0.40). This data suggests that oxytocin signaling in astrocytes may be a key player in the protection against depressive-like behaviors induced by oxytocin in the context of social isolation.

**Disclosures:** **M. Selles:** None. **R.C. Froemke:** None. **M.V. Chao:** None.

**Poster**

**PSTR043. Animal Models of Mood Disorders: Neuromodulation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR043.12/LL9

**Topic:** G.05. Mood Disorders

**Support:** NIH Grant R01MH111276

**Title:** Modulatory effects of orexin/hypocretin on sleep/wakefulness, anhedonia, and neuroinflammation in a diurnal rodent model of Seasonal Affective Disorder

**Authors: *A. COSTELLO**, K. LINNING-DUFFY, J. S. LONSTEIN, L. YAN;
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**Abstract:** Seasonal affective disorder (SAD) is characterized by depressive symptoms during the fall and winter. While the behavioral and psychological effects of daytime light deficiency are well known, the underlying neural mechanisms are unclear. Previous work in our lab using diurnal Nile grass rats (*Arvicanthis niloticus*) demonstrates that compared to animals housed in summer-like bright light/dark cycle (brLD, 1000 lux), animals housed in winter-like dim light (dimLD, 50 lux) exhibit deficits in sleep quality and anhedonia, as well as neural consequences including reduced orexin and sex- and brain region-specific inflammation. The objective of the present study is to test the hypothesis that the sleep disturbances, anhedonia, and neuroinflammatory responses observed in animals housed in winter-like dimLD are due to attenuated orexinergic output. Using a programmable minipump (iPrecio; SMP-310R) delivering ICV orexin peptide in dimLD animals, we predicted that the increased orexin would alleviate deficits in sleep and anhedonia and reduce pro-inflammatory response in animals housed in dimLD. Male and female grass rats were housed in dimLD (14 hr dim light:10 hr dark) for 4 weeks and received 6 hours of daily minipump-driven ICV infusion of orexin-A (OXA) in week 4 at the start of their light phase (ZT0-ZT6). Control animals housed in dimLD received infusion of vehicle (aCSF). In-cage locomotor activity and sleep/wakefulness were continuously monitored using infrared motion sensors and a piezoelectric system. A saccharin-solution preference (SSP) test was performed at the end of the infusion to assess anhedonia. Compared to vehicle-treated controls, OXA-treated animals had longer sleep bouts throughout the night, indicating improved sleep quality, and higher SSP, indicating reduced anhedonia. Following the

SSP test, brains were collected for immunohistology and qPCR to analyze markers of neuroinflammation. Data from males are still being collected, but data obtained in females suggest that OXA treatment decreases the microglia activation marker CD11b in the CA1, decreases IL-6 in the medial prefrontal cortex, and increases TNF-a expression in the basolateral amygdala. This study provides further understanding of the orexinergic system as a therapeutic target in light-induced neuroinflammatory-related disorders, such as SAD, as well as the mechanisms through which light influences the brain and behavior.

**Disclosures: A. Costello:** None. **K. Linning-Duffy:** None. **J.S. Lonstein:** None. **L. Yan:** None.

**Poster**

**PSTR043. Animal Models of Mood Disorders: Neuromodulation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR043.13/LL10

**Topic:** G.05. Mood Disorders

**Title:** Characterization of multiple progesterone withdrawals in intact and ovariectomized rats in experimental anxiety and depression.

**Authors: *D. ISLAS-PRECIADO**, E. ESTRADA-CAMARENA;
Lab. de Neuropsicofarmacología, Dirección de Investigaciones en Neurociencias, Inst. Nacional De Psiquiatría "Ramón de la Fuente Muñíz", Mexico City, Mexico

**Abstract: Introduction** Experimental approximations to study premenstrual anxiety and depression have been focused on a single induction of progesterone withdrawal (PW), that could affect construct validity, as the progesterone drop occurs in a repeated manner due to menstrual cycle. Thus, we aimed to characterize the effect of multiple PW on anxiety and depressive-like behavior in different models in intact and ovariectomized to assess the consistency of PW in both endocrine conditions. Stress response was determined through allopregnanolone (ALLO) and corticosterone (CORT) peripheral levels. **Method** Intact and ovariectomized Wistar rats were treated with 2mg/kg of progesterone for 5 consecutive days with a 48h washout period, until completion of 3 cycles of PW. Twenty-four hours after the last progesterone administration, animals were tested in the elevated-plus maze (EPM), light-dark test (LDT), and open field test (OFT). The behavioral despair was evaluated 48h after the last progesterone injection in the forced swimming test (FST). Behavioral assessments occurred in every PW cycle. **Results** PW increased anxiety-like behavior in OVX in EPM, while in intact the anxiogenic effect was observed in LDT. The PW increased behavioral despair in OVX rats in the first cycle of PW ($p<0.05$). Interestingly, PW induced higher immobility in the 1$^{st}$ PW in OVX, while in intact animals subsequent PW increased immobility behavior ($p<0.05$). CORT increased in OVX rats regardless of PW ($p<0.05$). ALLO was increased in PW animals in intact and OVX rats after FST exposure ($p<0.05$). **Conclusion** The anxiogenic effect of multiple PW was observed depending on the behavioral model. Multiple PW could increase vulnerability to behavioral despair. PW may induce ALLO and significantly increased in response to stress due to FST, perhaps as a stress-

compensatory mechanism. The potential effect of re-exposure to behavioral assessments cannot be disregarded. These results may help improve the preclinical models' construct validity to evaluate premenstrual anxiety and depression.

**Disclosures: D. Islas-Preciado:** None. **E. Estrada-Camarena:** None.

**Poster**

**PSTR043. Animal Models of Mood Disorders: Neuromodulation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR043.14/LL11

**Topic:** G.05. Mood Disorders

**Support:** NIMH R01-111604
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NINDS R01-085171

**Title:** Androgen Receptors in vHPC projection neurons to NAc regulates sex-specific responses to stress

**Authors: *I. LAKIC**[1], E. WILLIAMS[2], R. M. BASTLE[4], I. S. MAZE[5], A. J. ROBISON[3]; [1]Michigan State Univ., Haslett, MI; [3]Neurosci., [2]Michigan State Univ., East Lansing, MI; [4]Ichan Sch. of Med. at mount Siani, New York, NY; [5]Home, Icahn Sch. of Med. At Mount Sinai, Ossining, NY

**Abstract:** Androgen Receptors in vHPC projection neurons to NAc regulates sex-specific response to stress
Authors: Ivana Lakic, Elizabeth Williams, Ryan Bastle, Ian Maze, AJ Robison
Depression is a leading cause of disability in the U.S and is nearly twice as prevalent in females as it is in males, but the molecular underpinnings of this discrepancy remain unclear. We previously showed that female mice have higher baseline excitability in ventral hippocampal (vHPC) neurons projecting to the nucleus accumbens (NAc) than do males, and that this higher excitability causes susceptibility to stress-induced anhedonic behavior (Williams et al., *Biol Psych*, 2020). This work also showed that the sex differences in both excitability and anhedonic responses to stress are dependent on adult testosterone, but the mechanisms of these testosterone effects are unknown. Neurons in the vHPC strongly express androgen receptors (ARs) which are capable of affecting cell excitability. Thus, the present study examined whether testosterone-mediated resilience to stress-induced anhedonia in mice is dependent on AR expression specifically in the vHPC-NAc circuit. Using a novel intersecting viral strategy, we knocked out AR expression specifically in vHPC cells projecting to NAc in transgenic Cre-inducible Rosa-eGFP-L10a male mice floxxed for AR, then exposed them to subchronic variable stress (SCVS)

or chronic unpredictable stress (CUS). We then used a battery of behavioral tests to examine the role of vHPC-NAc AR expression in responses to stress, including sucrose preference as a measure of anhedonic responses. Circuit-specific AR knockout was validated using dual label immunofluorescence. We found that knocking out the AR in the vHPC-NAc decreased sucrose preference compared to AR intact controls in stressed males. Furthermore, in order to understand the molecular mechanisms driving sex differences in vHPC-NAc excitability, we used RT-PCR to examine gene expression differences in the vHPC from adult male and female non-treated, gonadectomized, DHT treated, and/or and stressed mice. We found that baseline gene expression differences are seen in the vHPC with differential expression seen in *KCCN3, CACNA1D, CHr1, CHr2,* and *SVIL*. These genes are involved in both cell excitability and stress responses. Taken together, these data results provide exciting new avenues to study sex-specific hormone-driven changes in brain circuit function driving behaviors central to depression and may provide insight for future gene targets for therapeutic intervention in mood disorders.
**Keywords:** stress, depression, androgen receptor, sex differences, nucleus accumbens, ventral hippocampus

**Disclosures: I. Lakic:** None. **E. Williams:** None. **R.M. Bastle:** None. **I.S. Maze:** None. **A.J. Robison:** None.

**Poster**

**PSTR043. Animal Models of Mood Disorders: Neuromodulation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR043.15/LL12

**Topic:** G.05. Mood Disorders

**Support:** R01 MH111604

**Title:** Sex hormones modulate ventral hippocampal control of nucleus accumbens neuronal activity

**Authors: *S. SIMMONS**[1], C. SUGIMOTO[2], A. EAGLE[2], A. ROBISON[2];
[2]Physiol., [1]Michigan State Univ., East Lansing, MI

**Abstract:** Sex-differences in the expression of symptoms across anxiety and major depressive disorders is well established through epidemiological studies. However, the underlying molecular mechanisms driving these differences across stress-responsive circuitry are not well understood. Several studies have implicated ventral hippocampus (vHipp) glutamatergic projections to the nucleus accumbens (NAc) as a key modulator of depressive-like behavior in males. Our group has shown that sex-specific differences in the excitability of vHPC-NAc projecting neurons drive susceptibility to anhedonia-like behavior following subchronic variable stress (SCVS). Importantly, chemogenetic alteration of the excitability of this projection or the sex-hormone status of the mouse (orchiectomy with and without testosterone replacement in males, or testosterone treatment in females) had opposing effects on anhedonia-like behaviors

following sub-chronic variable stress across sex. We now have preliminary data indicating that androgen receptor (AR) is highly expressed in the vHPC CA1 subregion and significantly alters intrinsic excitability of these neurons in male mice. Here, we explored the effects of vHPC neuron excitability on NAc ensemble activity utilizing *in vivo* cell type-specific calcium imaging. We determine whether testosterone- or AR-dependent changes in vHPC neuron excitability drive differential activation of D1- or D2-type medium spiny neurons in the NAc in awake and behaving male and female mice. Moreover, vHPC neurons also project to basolateral amygdala (BLA) to regulate anxiety-like behaviors and fear learning. Therefore, future directions will investigate the roles of sex hormones and stress on vHPC modulation of ensemble activity in both NAc and BLA while mice are assessed in both anxiety-like and motivated behaviors.

**Disclosures: S. Simmons:** None. **C. Sugimoto:** None. **A. Eagle:** None. **A. Robison:** None.

**Poster**

**PSTR043. Animal Models of Mood Disorders: Neuromodulation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR043.16/LL13

**Topic:** G.05. Mood Disorders

**Title:** Estrogen administration and withdrawal in a model of hormone-simulated pregnancy leads to alterations in behavior and gene expression but does not induce depression-like phenotypes in mice

**Authors:** K. BUCKHAULTS, ***B. SWACK**, B. SACHS;
Villanova Univ., Villanova, PA

**Abstract:** Pregnancy and the post-partum period are associated with substantial fluctuations in hormone levels and are frequently associated with significant stress. Many individuals also experience affective disturbances during the peri-partum period, including anxiety, the ‘baby blues,’ and post-partum depression. However, the extent to which these affective changes result from rapidly altering hormone levels, increased stress, or the combination of both remains largely unknown. The current study sought to evaluate the consequences of pregnancy-like hormonal changes on behavior and gene expression in c57BL6 mice in the absence of stress using a hormone-simulated pregnancy model. Our results reveal that animals receiving hormone injections to simulate the high levels of estrogen observed in late pregnancy and animals withdrawn from estrogen to mimic the rapid decline in this hormone following parturition both exhibit increased anxiety-like behavior compared to ovariectomized controls in the novel open field test. However, no other significant anxiety- or depression-like alterations were observed in either hormone-treated group compared to ovariectomized controls. Both hormone administration and estrogen withdrawal were shown to induce several significant alterations in gene expression in the bed nucleus of the stria terminalis and the periventricular nucleus of the hypothalamus. In contrast to the estrogen withdrawal hypothesis of post-partum depression, our

results suggest that this method estrogen withdrawal following hormone-simulated pregnancy in the absence of stress does not induce phenotypes consistent with postpartum depression in c57BL/6 mice. However, given that estrogen withdrawal does lead to significant gene expression changes in two stress-sensitive brain regions, it remains possible that estrogen withdrawal could still contribute to affective dysregulation in the peripartum period by influencing susceptibility to stress. Future research is required to evaluate this possibility.

**Disclosures:** **K. Buckhaults:** None. **B. Swack:** None. **B. Sachs:** None.

**Poster**

**PSTR043. Animal Models of Mood Disorders: Neuromodulation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR043.17/LL14

**Topic:** G.05. Mood Disorders

**Support:** Oscar Stern Award/Eisenberg Family Depression Center University of Michigan to NCT

**Title:** Regulation of stress and mood in a mouse model of oral contraceptives

**Authors: *K. M. SCHUH**[1], J. AHMED[2], E. KWAK[2], C. XU[2], N. C. TRONSON[3];
[1]Univ. of Michigan Psychology Grad. Program, Ann Arbor, MI; [2]Psychology, Univ. of Michigan, Ann Arbor, MI; [3]Psychology, Univ. of Mchigan, Ann Arbor, MI

**Abstract:** Hormonal contraceptives, including oral contraceptives (OCs) are a critical part of healthcare, with broad health and economic benefits. For many users, OCs have beneficial mood effects, with decreased premenstrual mood changes and overall improved mood. Yet for 4-10% of people, OCs trigger adverse mood effects and increased risk for depression. We used a mouse model of OC exposure, newly developed in our laboratory, to identify how commonly used OC formulations regulate stress responses and contribute to the vulnerability to stress-induced behavioral changes. In this project, we aimed to understand the mechanisms by which OCs modify the hypothalamic-pituitary-adrenal (HPA) axis. Female C57Bl6/N mice were given ethinyl estradiol (EE, 0.02μg) and levonorgestrel (LVNG, 0.75μg)- daily in 0.25mL 10% sucrose; control animals received 0.25mL of 10% sucrose. All treatments were given for at least 2 weeks prior to, and throughout, behavioral testing. At these doses, EE+LVNG suppresses the estrous cycle, has no gross effects on locomotor activity, and does not increase anxiety-like behavior. However, EE+LVNG does decrease sucrose preference suggesting a specific anhedonia-like effect and increases risk-assessment behavior suggesting more subtle changes in anxiety-related processes. Consistent with reliable findings from people using OCs, mice treated with EE+LVNG, show a significantly blunted acute stress response, as measured by corticosterone levels. Here, we hypothesize that OCs increase levels and expression of FKBP5, which in turn blunts the peripheral stress response. We determined OC-induced changes in glucocorticoid receptors, mineralocorticoid receptors, and FKBP5 levels/expression in the

paraventricular nucleus, amygdala, and hypothalamus to identify molecular mechanisms by which OCs interact with stress. Together these findings demonstrate that the modulation of the HPA axis are key mechanisms for vulnerability and resilience to OC-triggered depression. Identifying individual differences in stress responsivity may help predict which individuals will benefit from which OC formulations, improving precision medicine.

**Disclosures: K.M. Schuh:** None. **J. Ahmed:** None. **E. Kwak:** None. **C. Xu:** None. **N.C. Tronson:** None.

**Poster**

**PSTR043. Animal Models of Mood Disorders: Neuromodulation**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR043.18/LL15

**Topic:** G.05. Mood Disorders

**Support:** R01 DA048280

**Title:** Effects of chronic unpredictable stress, corticosterone and REDD1 overexpression in the prelimbic prefrontal cortex on conditioned approach behavior in rats

**Authors: *D. OLIVEIRA**[1], B. KURTOGLU[1], M. K. ESTES[1], L. J. LASKOWSKI[1], D. B. NOWAK[1], M. MANTYCH[2], D. S. WHEELER[2], B. WINDSOR[1], E. V. NEWENHIZEN[1], M. C. HEARING[2], R. A. WHEELER[2], J. R. MANTSCH[1];
[1]Phamacology and Toxicology, Med. Col. of Wisconsin, Milwaukee, WI; [2]Biomed. Sci., Marquette Univ., Milwaukee, WI

**Abstract:** Approach motivation is a construct under the positive systems domain of the NIMH Research Domain Criteria (RDoC) that includes cue-directed behavior. Deficits in approach motivation are an understudied aspect of chronic stress-related disorders, such as major depressive disorder (MDD) and likely involve synaptic and structural alterations in the prefrontal cortex. Glucocorticoid increases in REDD1 (regulated in development and DNA damage responses-1; aka, DDIT4/RTP801) and the resulting disruption of mTORC1 (mammalian target of rapamycin complex-1) function have been implicated in the effects of chronic stress on the prefrontal cortex. The present study investigated the contribution of corticosterone (CORT) and increased REDD1 expression in the prelimbic cortex (PrL) to chronic unpredictable stress (CUS) induced deficits in conditioned approach behavior, as assessed using Pavlovian autoshaping in adult, male Sprague Dawley rats (3-4 months old). CUS (twice daily stress exposure over 14 days) or oral exposure to 50 µg/mL of CORT over 14 days in the drinking water selectively reduced cue-directed behavior ($P < 0.001$) as assessed in the autoshaping task. Consistent with previously reported post-mortem measurements of REDD1 in the DLPFC of individuals diagnosed with MDD, CUS increased PrL REDD1 expression and decreased phosphorylation of Raptor ($P < 0.01$), a key regulatory protein for the stability and function of mTORC1, measured 4 hours post-CUS. To examine the impact of REDD1overexpression on conditioned approach and

PrL regulation, we injected AAV9-CaMKII-REDD1-mCherry or control AAV into the PrL, 4 weeks prior to testing for autoshaping. The effects of PrL REDD1 overexpression on cue-directed behavior will be reported. Finally, CUS produced deficits in excitatory transmission in layer V pyramidal neurons in the PrL that project to the nucleus accumbens core, suggesting that chronic stress causes CORT-mediated motivational deficits by increasing REDD1 levels and decreasing mTOR1 signaling in PrL pyramidal neurons that comprise a key output pathway to the nucleus accumbens. Ongoing studies are examining effects in female rats. These findings have implications for our understanding of stress-related disorders such as MDD and have the potential to guide novel therapeutic approaches.

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**Poster**

**PSTR044. Preclinical Models of Anxiety**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR044.01/LL16

**Topic:** G.06. Anxiety Disorders

**Support:** R01-MH126443

**Title:** Inhibition of methylation of H3K9 rescues anxiety induced by adolescent social isolation in female mice

**Authors: *P. LI**, Z. YAN;
State Univ. of New York, Buffalo, Buffalo, NY

**Abstract:** Social isolation during adolescence has been found to increase the risk of mental disorders. However, the epigenetic mechanisms underlying neuropsychiatric disorders caused by social isolation remain unclear. Here we found 6-week social isolation (SI) after weaning causes anxiety in adult female mice. Increased methylation of histone H3 at lysine 9 (H3K9) and its methyltransferase, SUV39H1 and SETDB1, are observed in prefrontal cortex (PFC) in SI female mice. Additionally, SI significantly elevates the gene levels of GABA receptor, Gabrb2/g2/d, and reduces neuronal excitability. SI also reduces the release of neurotransmitters, as evidenced by decreased mRNA level of STX1A, and lowered neuronal activity, as indicated by reduced expression of immediate early genes, Npas4, Arc, and C-Fos. Besides, SI increases H3K9me2 occupancy around Arc enhancer, which causes the decreased expression of Arc. Furthermore, we found that inhibiting H3K9-specific methyltransferase with the compound UNC-0642 attenuates anxiety. Mechanistically, it recovers the neuronal activity. Our results shed light on a novel epigenetic mechanism and a potential therapeutic target for anxiety induced by chronic social isolation in adolescence.

**Disclosures:** **P. Li:** None. **Z. Yan:** None.

**Poster**

**PSTR044. Preclinical Models of Anxiety**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR044.02/LL17

**Topic:** G.06. Anxiety Disorders

**Support:** Guangxi Science and Technology Major Project (AA18118049-5)
RGC Areas of Excellence (AoE/P-705/16)

**Title:** Camellia nitidissima Chi extract promotes adult hippocampal neurogenesis and attenuates chronic corticosterone-induced depressive behaviours through regulating Akt/GSK3β/CREB signaling pathway

**Authors: *B. TSOI**[1,2], C. GAO[3,2], S. YAN[2], Q. DU[2], H. YU[4], P. LI[4], J. DENG[5], J. SHEN[2]; [1]Dept. of Food Sci. and Nutr., Hong Kong Polytechnic Univ., Hung Hom, Hong Kong, Hong Kong; [2]The Univ. of Hong Kong, Hong Kong, Hong Kong; [3]Zhenjiang Univ. City Col., Zhejiang, China; [4]Univ. of Macau, Macau, Macao; [5]Guangxi Univ. of Chinese Med., Guangxi, China

**Abstract:** Hormonal imbalance causes depressive behaviours in chronic mental disorders. The use of natural products to relieve depressive symptoms is getting attention due to its minimal side effects and multiple health benefits. The present study aims to test the hypothesis that Camellia nitidissima Chi leave extract (CNC) could have antidepressant effects and whose underlying mechanisms could be related to promote hippocampal neurogenesis. Firstly, we conducted quality control study and identified 17 active compounds in the CNC extract. Then, we performed a series of behaviour tests to evaluate the antidepressant effects in a chronic corticosterone (CORT)-induced depressive mouse model. CNC extract significantly ameliorated CORT-induced depressive behaviours, whose effects were similar to sertraline. Interestingly, CNC extract decreased the levels of CORT and ACTH in the plasma and increased 5-HT in plasma and hippocampus. CNC extract promoted adult hippocampal neurogenesis in the CORT-treated mice in vivo. The neurogenic effects of CNC were also confirmed in primary cultured hippocampal neurons and hESCs with CORT challenge in vitro. Furthermore, CNC enhanced the phosphorylation of Akt, GSK3β and CREB in the hippocampus of CORT-treated mice in vivo as well as CORT-treated PC12 cells in vitro. Co-treatment of wortmannin abolished the effects of CNC. Taken together, CNC could be an effective functional food to stimulate hippocampal neurogenesis for anti-depressant treatment. The neurogenic mechanisms could be related to regulating hypothalamic-pituitary adrenal axis and activating Akt/GSK3β/CREB signaling pathway.

**Disclosures:** **B. Tsoi:** None. **C. Gao:** None. **S. Yan:** None. **Q. Du:** None. **H. Yu:** None. **P. Li:** None. **J. Deng:** None. **J. Shen:** None.

**Poster**

**PSTR044. Preclinical Models of Anxiety**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR044.03/LL18

**Topic:** G.06. Anxiety Disorders

**Support:** Colby College Psychology Department
Maine INBRE GR1019

**Title:** Preferred recovery method of Sprague-Dawley rats following a stressful experience depends on nicotine exposure and social environment

**Authors: M. MACOMBER**, S. VILLAGOMEZ, J. LAGOMARSINO, D. HICKMAN, S. STRINE, A. DOAK, M. J. GLENN, *C. EVANGELISTA;
Psychology, Colby Col., Waterville, ME

**Abstract:** With the high prevalence of anxiety disorders, there is a major need to understand how their development and persistence can be mitigated. After a stressful experience, various coping mechanisms can be utilized such as drug use and seeking social support. For example, people may consume nicotine by smoking cigarettes or vaping. Alternatively, they may chat with family, friends, or even strangers. Recovery methods can be combined such as smoking and chatting with a friend. The use of these coping mechanisms varies among individuals and has been reported to have contrasting effects on fear memory and feelings of anxiety. How is preference for nicotine as a stress recovery method influenced by social environments? How do these recovery preferences affect extinction learning and anxiety-like behavior? To investigate how nicotine exposure and social environments interact to shape preferred stress recovery methods, 96 Sprague-Dawley (M = 48, F = 48) were presented with stressful events followed by recovery periods. During the stress induction phase, rats were presented with white noise (WN) that co-terminated with a mild (0.8 mA) footshock. Immediately after was the recovery phase, during which rats were injected subcutaneously with saline or nicotine (0.1 mg/kg) and then placed in one side of a 2-chamber conditioned place preference (CPP) box. They recovered in the CPP chamber either alone, with their cagemate (friend), or with a rat from a different cage (stranger). To assess recovery preference, rats underwent the stress induction phase and then were placed in the CPP box with both the nicotine- and saline-paired chambers accessible. We found that rats preferred to recover in contexts associated with nicotine alone or with a stranger. In contexts associated with a friend, female rats showed no recovery preference while male rats preferred the saline-paired chamber. We tested the effects of preferred recovery contexts on fear extinction to the WN and the anxiolytic effects of nicotine using the open field test but there were no significant findings. Overall, these results highlight the complex interplay between nicotine and social environments in shaping recovery preferences. These data have led us to further investigate whether rats prefer to recover with nicotine in the context of a friend or stranger and the influence of these recovery methods on fear extinction and anxiety-like behavior. Elucidating the interactive effects of different recovery methods (e.g., nicotine and

social environments) can help us better understand preferred coping mechanisms in response to stressful events and their lasting effects on fear memories and anxiety.

**Disclosures: M. Macomber:** None. **S. Villagomez:** None. **J. Lagomarsino:** None. **D. Hickman:** None. **S. Strine:** None. **A. Doak:** None. **M.J. Glenn:** None. **C. Evangelista:** None.

**Poster**

**PSTR044. Preclinical Models of Anxiety**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR044.04/LL19

**Topic:** G.06. Anxiety Disorders

**Support:** Midwestern University

**Title:** Chronic mild stress leads to anxiety-like behavior and decreased p70 S6K1 activity in the hippocampus and medial prefrontal cortex of male C57/Bl6 mice

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**Abstract:** Chronic stress can have a wide variety of negative effects on physical and psychological well-being, including increased anxiety and depressive clinical symptoms. An estimated 31.2% of adults in the United States experience an anxiety disorder at some point in their lives. Previous studies demonstrate that p70 S6 kinase 1 (S6K1), a mTORC1 downstream effector, influences anxiety-like and depression-like behavior in rodent models; however, exceedingly few studies have investigated the involvement of S6K1 in chronic stress and anxiety. Using a four-week chronic mild stress (CMS) paradigm in adult male C57/Bl6 mice, we demonstrate that CMS results in anxiety-like behavior on the elevated plus maze and the open field task. Western blotting analysis of the prefrontal cortex and hippocampus of CMS mice and their wild-type littermates showed a decrease in phosphorylated to total ratios of S6 ribosomal protein, suggesting downregulation of S6K1 activity. Using PF-4708671, a selective inhibitor of S6K1, we demonstrate that downregulation of S6K1 is sufficient to induce anxiety-like behavior in the elevated plus maze and open field compared to vehicle treated mice. Our results demonstrate that decreased activity of S6K1 results in anxiety-like behavior in mice, supporting the role of S6K1 in the pathogenesis of anxiety-like behavior in male mice.

**Disclosures: J. David:** None. **K. Trombetti:** None. **E. Ruben:** None. **M. Ruben:** None. **P. Suorsa:** None. **C. Neilsen:** None. **J. Thiessen:** None. **M. Mousset:** None. **P. Chu:** None. **T.N. Huynh:** None.

**Poster**

**PSTR044. Preclinical Models of Anxiety**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR044.05/LL20

**Topic:** G.06. Anxiety Disorders

**Support:** NIDA Grant DA041482
NIDA Grant DA047678

**Title:** A neuronal coping mechanism linking stress-induced anxiety to motivation for reward.

**Authors: *P. M. KLENOWSKI**[1], R. ZHAO-SHEA[2], T. FREELS[1], S. MOLAS[3], M. ZINTER[1], P. M'ANGALE[4], C. XIAO[1], T. THOMSON[5], A. R. TAPPER[3];
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**Abstract:** Stress-coping involves innate and active motivational behaviors that reduce anxiety under stressful situations. However, the neuronal bases directly linking stress, anxiety, and motivation for reward are largely unknown. Here, using in vivo fiber photometry, we show that acute stressors activate mouse GABAergic neurons in the interpeduncular nucleus (IPN). Monitoring dynamic activity patterns of IPN GABAergic neurons revealed that stressor-induced increases in activity were opposed by stress-coping behaviors including self-grooming, as well as by sucrose reward consumption. Optogenetic silencing IPN GABAergic neuron activation during acute stress episodes mimicked coping strategies and alleviated anxiety-like behavior. Interestingly, reduction of IPN neuronal activity during sucrose consumption was increased with larger stressors, suggesting that acute stressors may motivate reward-seeking to decrease IPN activity. Using a mouse model of stress-enhanced motivation for sucrose seeking, we found that photoinhibition of IPN GABAergic neurons reduced stress-induced motivation for sucrose; whereas, photoactivation of IPN GABAergic neurons or excitatory inputs from medial habenula potentiated sucrose seeking. Single cell-sequencing, fiber photometry, and optogenetic experiments revealed stress-activated IPN GABAergic neurons that drive motivated sucrose seeking express somatostatin. Together, these data suggest that stress induces innate behaviors and motivates reward-seeking to oppose IPN neuronal activation as an anxiolytic stress-coping mechanism.

**Disclosures: P.M. Klenowski:** None. **R. Zhao-Shea:** None. **T. Freels:** None. **S. Molas:** None. **M. Zinter:** None. **P. M'Angale:** None. **C. Xiao:** None. **T. Thomson:** None. **A.R. Tapper:** None.

**Poster**

**PSTR044. Preclinical Models of Anxiety**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR044.06/LL21

**Topic:** G.06. Anxiety Disorders

**Title:** Asprosin, a metabolic hormone, modulates anxiety-like behavior

**Authors: *B. BASU**, I. MISHRA, A. QIAN, S. HANUMANTHU, G. NAVEH, A. CHOPRA; Case Western Reserve Univ., Cleveland, OH

**Abstract:** Although anxiety disorders have a lifetime prevalence of almost 30%, few therapeutic targets have been identified. Strikingly, obesity is particularly associated with substantially increased risk for anxiety with a prevalence rate of 40%. Furthermore, obese rodents, whether by virtue of a high fat diet or genetic predisposition to obesity, also display increased anxiety-like behavior. The mechanistic link for the relationship between obesity and anxiety, however, is unknown. In 2016, our lab discovered asprosin, a fasting-induced hormone that is highly expressed in adipose tissue. Upon secretion, asprosin stimulates appetite and hepatic glucose release. Asprosin is a ~30 kDa C-terminal cleavage product of fibrillin-1 that normally circulates in cerebrospinal fluid (CSF) and plasma at nanomolar levels, and is significantly elevated in obesity. Importantly, we have demonstrated that anti-asprosin monoclonal antibodies (mAbs) are a dual-effect pharmacologic therapy that targets the two key pillars of metabolic syndrome (MS) - overnutrition and blood glucose burden with obesity. Recently we have also identified the neural target for asprosin, Protein tyrosine phosphatase receptor δ (Ptprd), which is highly expressed throughout the brain. This study suggests that elevated levels of asprosin promote anxiety, thereby providing a potential mechanistic link with obesity and a potential therapy. Specifically, my results indicate that (1) pharmacologic asprosin neutralization mitigates anxiety-like behavior regardless of metabolic state (2) genetic inhibition of asprosin and its receptor leads to decreased levels of anxiety (3) asprosin neutralization is an effective treatment in treating anxiety. Future studies will delineate the central circuit necessary for asprosin-mediated modulation of anxiety. My studies thus far suggest a novel function of asprosin in the control of anxiety, and that the anti-asprosin mAb could be a novel anxiolytic agent that may have particularly enhanced benefits for individuals with obesity-associated anxiety, significantly improving the quality of life in these individuals.

**Disclosures: B. Basu:** None. **I. Mishra:** None. **A. Qian:** None. **S. Hanumanthu:** None. **G. Naveh:** None. **A. Chopra:** None.

**Poster**

**PSTR044. Preclinical Models of Anxiety**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR044.07/LL22

**Topic:** G.06. Anxiety Disorders

**Support:** São Paulo Research Foundation (FAPESP) Grant 2022/10168-5
NIH R01 AA028879

P60 AA006420
T32 AA007456
Pearson Center for Alcoholism and Addiction Research

**Title:** Impacts of repeated predator odor stress on ethanol intake, anxiety-, depressive- and irritability-like behaviors in adult mice

**Authors: *C. FAVORETTO**[1,4], K. LIN[1], A. NGUYEN[2], G. CHACON[1], A. J. ROBERTS[3], T. NADAV[3], S. RANJAN[1], L. B. BERTOTTO[1], F. C. CRUZ[5], E. P. ZORRILLA[1];
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**Abstract:** Repeated stress is a risk factor for the development of alcohol use and emotional disorders, which severely impact health, disability, and well-being worldwide. Chronic intermittent ethanol (CIE) vapor exposure is a widely used predictive animal model that induces ethanol dependence over several weeks via adaptations in reward, stress, and decision-making circuitry. Here, we test the hypothesis in mice that exposure to rat predator odor, a model of psychosocial stress, promotes the development of 1) increased ethanol intake or preference in the CIE model and 2) anxiety-, depressive-, or irritability-like behaviors. In experiment 1, adult male C57BL/6J mice (n=8-10/group) were subjected to 3 cycles of 4-day exposure to CIE vapor (16h on/ ascending blood ethanol level targets 100-250 mg/dl) or Air, alternated with 5-day access to 2-bottle choice voluntary ethanol intake (15% w/v). During the last two drinking cycles, mice received 30-min predator odor stress or control cage exposure immediately before each drinking session. In ongoing experiment 2, adult male and female TRAP2-Ai9 reporter mice received 10 exposures to predator odor or control cage and then were successively tested 3-14 days post-stressor for elevated plus maze, marble burying, bottle brush, light-dark box, “supersac” preference (3% glucose + 0.125% saccharin), and sucrose splash behaviors (n=5-15/group). As expected, CIE exposure increased ethanol intake by the 3rd cycle in unstressed mice. A stress x CIE x time interaction showed that stressed-CIE mice presented increased ethanol intake vs. their stressed-Air control earlier - by the 2nd cycle. Unexpectedly, predator odor reduced ethanol preference ratios irrespective of CIE vs. Air condition, with increased water intake. Data in experiment 2 so far show that repeated stress decreased the number of marbles buried in the marble burying test and defensive behaviors in the bottle brush test. Moreover, predator odor increased the latency to enter the light side in the light-dark box test and reduced preference for “supersac” solution. Also, females showed increased “supersac” intake and preference vs. males. However, no stress or sex effects were detected for parameters evaluated in the elevated plus maze and sucrose splash tests. In sum, predator odor stress accelerated CIE-induced increase in ethanol intake. In addition, repeated stress reduced compulsive-like marble burying, defensive-like responses to a bottle brush, and preference for “supersac” reward, and increased anxiety-like behavior during exploration in the light-dark box. Further collection of behavioral data and striatal ensembles TRAPped during stress are in process.

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**Poster**

**PSTR044. Preclinical Models of Anxiety**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR044.08/LL23

**Topic:** G.06. Anxiety Disorders

**Support:** Enhancing Undergraduate Research & Creative Activities

**Title:** Probiotics produce anxiolytic effects but not antidepressant effects in the chick social-separation stress test, a dual-drug screening model of treatment-resistant depression

**Authors: *S. W. WHITE**[1], H. M. CALLAHAN[1], S. J. SMITH[2];
[1]Psychology & Philosophy, Sam Houston State Univ., Huntsville, TX; [2]Dept. of Neurosci., Univ. of Florida, Gainesville, FL

**Abstract:** Pre-clinical and clinical studies suggests that probiotics can produce anxiolytic and/or antidepressant effects. However, these effects have not been evaluated in a pre-clinical model of treatment-resistant depression. The chick social-separation stress paradigm is a dual-drug screening assay that produces both an anxiety-like phase followed by a depression-like phase. Utilizing this paradigm, the goal of this study was to evaluate the potential anxiolytic and/or antidepressant effects of probiotic administration in the stress-vulnerable, treatment-resistant Black Australorp genetic line. Male Black Australorps were housed under standard conditions and were divided into four treatment groups: saline-saline, probiotic-saline, saline-fluoxetine, and probiotic-fluoxetine. Each animal in a probiotic-treatment group received 450,000,000 CFUs of probiotic in 0.05 mL cold physiological saline orally twice daily. Fluoxetine 10 mg/kg was mixed and administered via i.p. once daily. Saline was administered both orally and/or via i.p. depending on treatment group. All treatments were administered for 9 days. On day 10, animals were exposed to a 90-minute isolation stressor and distress vocalizations (DVocs) were recorded. Separate one-way ANOVAs were conducted to determine anxiolytic or antidepressant effects. Post-hoc analysis using Fisher's LSD was conducted to determine specific group differences. The ANOVAs revealed a significant effect for probiotic treatment in the anxiety phase [$F(3, 38)=4.761$; $p = 0.006$]. Further analysis revealed a large effect size ($\eta_p^2 = .273$). Post-hoc analysis using Fisher's LSD revealed the probiotic-saline -treated group displayed significantly reduced DVoc rates compared to the saline-saline -treated group during the first five minutes of isolation indicative of an anxiolytic-like effect. This anxiolytic effect was absent in the saline-fluoxetine and probiotic-fluoxetine treatment groups. Statistical analyses failed to reveal a significant treatment effect for the depression phase for any of the treatment groups. Our results suggest that probiotics may be useful in treating the clinical population suffering from anxiety, particularly panic disorder. However, the co-administration of an SSRI may inhibit probiotic's anxiolytic effects. Our results also suggest that probiotics may not be a useful treatment option for those suffering from treatment-resistant depression.

**Disclosures: S.W. White:** None. **H.M. Callahan:** None. **S.J. Smith:** None.

**Poster**

**PSTR044. Preclinical Models of Anxiety**

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**Program #/Poster #:** PSTR044.09/LL24

**Topic:** G.06. Anxiety Disorders

**Support:** Puerto Rico Science, Technology, and Research Trust Catalyzer Grant
Institutional Funds for Research Development
PR INBRE
Puerto Rico - Louis Stokes Alliance for Minority Participation

**Title:** Discovery and Development of Anxiolytic Agents from Tropical Marine Macroalgae

**Authors: *G. ORTIZ**[1], G. RAMÍREZ[2], A. RIVERA[3], J. ALICEA[3], R. CRUZ[2], L. APONTE[4], A. GONZÁLEZ[1], G. DYER[5], E. CARO[5], R. CHIESA[2];
[1]Natural Sci., [2]Biol., [3]Chem., [4]Psychology, Univ. of Puerto Rico, Cayey, Puerto Rico; [5]UPR Med. Sci. Campus, San Juan, Puerto Rico

**Abstract:** Surveys show that one-third of the population is affected by an anxiety disorder. These are mostly treated with benzodiazepines, which can induce dependence disorders through tolerance and resistance mechanisms. This highlights the need for safer and more effective anxiolytic drugs. Recently, marine natural products have proven to be a rich chemical space for drug discovery and development. Specifically, tropical marine algae produce a wide range of metabolites with diverse biological activity, including neuroprotection. We propose to study the anxiolytic effects of natural products derived from marine tropical brown algae using the invertebrate fly model *Drosophila melanogaster*. Our research aims to chemically characterize brown algae extracts, use these extracts for anxiety-related behavioral tests using *D. melanogaster*, and identify the chemical components responsible for anxiolytic activity. The methodology consists of performing Open Field Tests using young adult flies to compare the behavior between the negative control group (n=48), which are not exposed to extracts, and the experimental groups (n=48), that include acute expositions (6 hours) and chronic expositions (oviposition to adulthood) to algae extracts. The parameter measured was the distance each fly traveled from the center of the Open Field Arena to the walls. To determine if the results of the experimental assays with each alga were statistically significant, we performed the Mann-Whitney U test and considered a p-value <0.05. We have previously reported anxiolytic effects in *D. melanogaster* after the chronic administration of the crude organic extract of *Stypopodium zonale*. Our recent data has proven that this alga has anxiolytic effects in acute expositions as well (p-value: <0.001); thus, its effect is comparable to the effect of diazepam, a benzodiazepine used as our positive control. Statistically significant anxiolytic effects were also obtained for *Dictyota cervicornis* (<0.001) and *Padina boergesenii* (<0.001) in chronic expositions, although no relevant anxiolytic effects were observed for *Ulva* (0.1650), *Symploca* (0.0345) and *Sargassum sp* (0.6869). Our research represents an unprecedented approach to anxiolytic drug discovery as it improves our understanding of Puerto Rico's marine algae and their natural products' chemo-diversity. In addition, to address the gap between safer anxiolytics and better models for their discovery, this project aims to assess the anxiolytic effects of marine algae

natural products in a *D. melanogaster* model to describe new anxiolytic agents and correlate behavioral anxiety to key biochemical pathways involved in anxiety disorders.

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**Poster**

**PSTR044. Preclinical Models of Anxiety**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR044.10/LL25

**Topic:** G.06. Anxiety Disorders

**Support:** NIMH R15MH127514
Brain and Behavior Research Foundation NARSAD

**Title:** Neural and behavioral effects of early life stress

**Authors: *J. RONQUILLO**[1], S. MAJUMDAR[2], L. HALLADAY[1];
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**Abstract:** Childhood neglect can induce deficits in reward, aversion, and social behaviors. Investigations into the neural mechanisms mediating early life stress-induced impairments have largely focused on dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and its release of the stress hormone corticotropin-releasing factor (CRF), but less is known regarding the role of extrahypothalamic neural substrates. To model early life stress, our lab uses a mouse maternal separation with early weaning (MSEW) protocol, which alters behavior across the lifespan. Previously, by using a variety of tools that allow us to record and manipulate neural activity, we have identified the bed nucleus of the stria terminalis (BNST) as a major regulator of the behavioral deficits observed in mice with a history of MSEW. We have published causal evidence that MSEW induces heightened activity in the BNST as seen through chemogenetic inhibition of BNST neurons which mitigates some of the behavioral deficits we observe. Likewise, chemogenetic excitation of BNST neurons in non-stressed control mice mimics behavioral deficits seen following MSEW. The overarching goal of our present work is to identify the neuronal circuits underlying MSEW-induced behavioral deficits, which include regions such as the BNST and the paraventricular nucleus of the hypothalamus (PVN). We are using a variety of tools including chemogenetics, in vivo electrophysiology, and immunohistochemistry to understand how MSEW alters neural circuitry to incite last effects on social behavior.

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**Poster**

**PSTR044. Preclinical Models of Anxiety**

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**Topic:** G.06. Anxiety Disorders

**Support:** NIH R21MH121836
NIH R01MH131053
PA CURE Grant SAP # 4100085747

**Title:** In vivo detection of prefrontal noradrenergic modulation during discrete approach-avoidance and aversive behaviors via fiber photometry

**Authors: *N. N. BOURAS**, N. R. MACK, W.-J. GAO;
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**Abstract:** Anxiety is the adaptive response to a stressful or unpredictable life event. This response can be helpful at times, but anxiogenic responses can also lead to distress and cognitive dysfunction depending on duration and intensity. Recent anxiety-related rodent and human studies have identified cortico-limbic dysfunction in several brain regions, including the prefrontal cortex (PFC), amygdala, and ventral hippocampus. The PFC plays a critical role in regulating anxiety. Disruption of this brain region results in impaired cognitive functioning, including deficits in flexible decision-making, similar to the effects seen in anxiety disorders. Norepinephrine (NE) is a neurotransmitter synthesized in the locus coeruleus (LC) and released in the PFC that is highly associated with arousal, attention, decision-making, stress, and anxiety. However, our understanding of the precise nature of NE signaling in the PFC and its contributions to anxiety-like behavior and cognitive dysfunction remains limited due to the difficulties associated with detecting NE *in vivo*. A recent study revealed that a novel fluorescent biosensor for NE, GRAB-NE, allows for specific *in vivo* detection of NE dynamics in real-time. We implemented fiber photometry to monitor changes in NE in the mouse prelimbic cortex using the GRAB-NE biosensor while mice engaged in approach-avoidance conflict tasks. In addition, changes in NE were evaluated during repeated exposure to an aversive foot shock fear conditioning and anticipatory fear behavior 24 hours following shock exposure. These approaches enabled us to detect prefrontal NE signals during discrete behavioral events and determine if NE dynamics in the PFC are related to anxiogenic states. Results suggest that NE signaling in the PFC shows opposing dynamics in fearful or anxiety-provoking contexts compared to safe contexts. These identified dynamics illustrate the importance of PFC-NE dynamics in anxiety-like and aversive behavior. This pre-clinical work may provide novel insight into possible therapeutic approaches involving alterations of brain-region- and circuit-specific neuromodulator activity.
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**Poster**

**PSTR044. Preclinical Models of Anxiety**

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**Program #/Poster #:** PSTR044.12/LL27

**Topic:** G.06. Anxiety Disorders

**Title:** Does Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP) Cause Anxiolytic Properties in the Rat Hippocampus?

**Authors: *K. SATO**[1], S. IWATA[1], T. HATAKEYAMA[1,2], G. WATANABE[1,2], R. OHTA[3], M. KAWAGUCHI[1];
[1]Lab. of Animal Behavior and Envrn. Sci., [2]Organization for the Strategic Coordination of Res. and Intellectual Property, Meiji Univ., Kanagawa, Japan; [3]Hatano Res. Inst., Food and Drug Safety Ctr., Kanagawa, Japan

**Abstract:** Hatano rats (high-avoidance animal, HAA; low-avoidance animal, LAA) are inbred strains derived from Sprague-Dawley (SD) rats based on the performance of avoidance learning tests. In elevated plus maze tests (EPM), anxiety-like behavior, which is defined as an avoidance of open arms in rodents, is higher in HAA than LAA. We previously demonstrated that in the hippocampus, the expression level of the Adenylate cyclase activating polypeptide (*Adcyap1*) gene, which encodes the pituitary adenylate cyclase activating polypeptide (PACAP), is lower in HAA than LAA, which suggests that PACAP in the hippocampus might inhibit anxiety-like behavior in LAA. Although intracerebroventricular administration of PACAP has been reported to increase anxiety-like behavior, the direct involvement of PACAP in the hippocampus has not been confirmed. Therefore, the aim of this study is to determine whether PACAP exhibits anxiolytic propertries of injecting the antagonist directly in the hippocampus of SD rats. To confirm the effects of drug administration, fear conditioning tests were conducted, since PACAP antagonists have been reported to decrease fear responses in the hippocampus. Cannulation surgery was performed on the hippocampus of 24 ten-week-old SD rats. Then at 11 weeks, behavioral tests were conducted after intrahippocampal administration of either a 40 pg/ml solution of the PACAP antagonist (PACAP-6-38) or 2 µl of artificial cerebrospinal fluid. An EPM test was conducted to measure the duration of open arm exploration, the number of open arm entries, and the total distance traveled in 5 minutes. In the fear conditioning test, rats received two foot-shocks (0.6 mA/sec) after a 2-minute habituation period, and then freezing behavior was measured for 3 minutes in the same apparatus 24 hours later. The cannula insertion site was confirmed using brain sectionings later. Only the individuals with cannula correctly inserted into the hippocampus were included in the analysis. The effect of the PACAP antagonist in the hippocampus was confirmed in all these subjects through the fear conditioning test. The EPM test showed that intrahippocampal administration of the PACAP antagonist showed anxiolytic effects rather than an increase in anxiety, with no effect on the total distance traveled. Therefore, contrary to our expectations, PACAP in the hippocampus of SD rats is suggested to have the potential to promote anxiety-like behavior.

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**Poster**

**PSTR044. Preclinical Models of Anxiety**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR044.13/LL28

**Topic:** G.06. Anxiety Disorders

**Support:** F32MH125597
IOS 1937335
R01MH121829

**Title:** Calcium imaging of the bed nucleus of the stria terminalis in aggressive and non-aggressive social contexts

**Authors: A. SERNA GODOY**[1], E. C. WRIGHT[3], P. LUO[4], H. C. ZAKHARENKOV[2], *B. C. TRAINOR[2];
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**Abstract:** Social anxiety is a common health condition that is more prevalent in women than men in adulthood. Adolescence is an important time period where this sex differences develop after puberty. The bed nucleus of stria terminalis (BNST) is an important nucleus modulating social approach and vigilance, behaviors that are stress-sensitive. This area is also known to present both functional and structural sex differences. The California mouse (*Peromyscus californicus*) is an ideal model species to study the sexual differentiation of stress responses. Prior research showed that gonadal hormones act during puberty to reduce immediate-gene responses in the BNST after stress. Here we use fiber photometry to measure calcium transients in the BNST during social interactions in threatening and non-threatening contexts. Males were randomly assigned to either a pre-pubertally castrated group or sham condition. When tested as adults, our results show that both castrated and sham mice showed increased activity when engaging in nose-to-nose sniffing with an aggressive mouse ($\beta$=10.22, z=2.05, p=0.04) while only castrated males showed increased activity when engaged in nose-to-nose sniffing with a non-aggressive mouse (Fig. 3E, $\beta$=13.2, z=2.23, p=0.03). The castrated group also showed increased calcium transients when engaging in anogenital sniffing with non-aggressive target mice ($\beta$=6.12, z=2.06, p=0.04) and when attacked by aggressive target mice ($\beta$=5.71, z=2.67, p=0.008). Importantly, neither group showed changes in neural activity during bouts of freezing behavior. These results demonstrate that gonadal hormones contribute to sexual differentiation of BNST responses by reducing activity in less threatening social contexts. Ongoing experiments are testing the extent to which these results generalize to females. Together these results shed light on how pubertal development shapes behavioral responses to social stressors in adulthood.

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**Poster**

**PSTR044. Preclinical Models of Anxiety**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR044.14/MM1

**Topic:** G.06. Anxiety Disorders

**Title:** Enhanced insight into threat memory acquisition by spatial gene expression profiling

**Authors: L. ROSTIN**, J. OTTEN, S. DAN, A. PROFETTO, R. LARDENOIJE, *T. KLENGEL;
McLean Hosp., Belmont, MA

**Abstract:** Maladaptive transcriptional alterations within complex neurocircuitries are central to many stress- and trauma-related disorders. However, how gene expression changes concertedly across brain regions remains largely unknown. We generated spatial transcriptomics RNAseq (stRNAseq) data in C57BL/6 mice exposed to auditory threat conditioning (n=8 per group), capturing the early memory consolidation period. Tissue sections at bregma -1.8 were placed on a 10X Visium chip and used for downstream analyses. RNAscope and AAV-mediated shRNA knockdown experiments provide additional insight into spatial gene regulation in threat conditioning. Unsupervised clustering analysis of stRNAseq data reveals 33 subregions in concordance with known anatomical structures. Cluster specific expression markers are in alignment with in-situ hybridization data of the Allen Brain Atlas. Differential gene expression analysis between threat conditioned and control animals results in a total of 415 DEGs (p.FDR < 0.05) across subregions and RNAscope analyses confirms the expression differences in selected subregions. In addition, network analyses show a coordinated transcriptional response to fear conditioning across multiple brain regions. We selected 4 genes (*Dek*, *Cep19*, *Aldh5a1*, and *Tsfm*) for AAV-mediated shRNA knockdown and provide further evidence for their function in threat memory formation. This includes an increase in fear expression in Cep19 knockdown animals. Our results indicate that multiple brain regions show a coordinated transcriptional response to threat conditioning. Knockdown of the selected genes provide evidence for their role in threat conditioning.

**Disclosures:** **L. Rostin:** None. **J. Otten:** None. **S. Dan:** None. **A. Profetto:** None. **R. Lardenoije:** None. **T. Klengel:** None.

**Poster**

**PSTR044. Preclinical Models of Anxiety**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR044.15/MM2

**Topic:** G.06. Anxiety Disorders

**Support:** NSERC PGS-D
Mitacs Canada
Artelo Biosciences

**Title:** A novel cannabidiol:tetramethylpyrazine (CBD:TMP) cocrystal improves the efficacy and bioavailability of cannabidiol to induce anxiolytic and anti-depressant effects

**Authors: *M. JONES**[1], T. C. UZUNESER[1], S. O'SULLIVAN[4], M. SARIKAHYA[2], A. YATES[4], W. J. RUSHLOW[5], S. R. LAVIOLETTE[3];
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**Abstract:** Cannabidiol (CBD), a principal constituent of the *Cannabis sativa* plant, is a drug that is gaining traction as a treatment option for neuropsychiatric disorders. Specifically, CBD displays anxiolytic (Masataka, 2019; Onaivi et al., 1990) and anti-depressant properties (Xu et al., 2019) with little to no psychotropic effects (Alves et al., 2020), suggesting it is a promising treatment avenue for anxiety and depressive disorders. However, the therapeutic utility of CBD is limited by its pharmacokinetic properties, including poor oral bioavailability, solubility, and stability (Brenneman et al., 2018; Xu et al., 2019). Therefore, a novel cocrystal of CBD with the co-former tetramethylpyrazine (TMP) was developed to modify the pharmacokinetic properties of CBD whilst retaining the pharmacological drug activity. TMP is a constituent of the *Ligusticum* plant species commonly used in Asian traditional medicine (Lin et al., 2022). This cocrystal is called CBD:TMP (or ART12.11). We sought to investigate the pharmacotherapeutic potential of CBD:TMP compared to CBD in the treatment of anxiety and depressive phenotypes. For this integrative research project, we investigated the dose-dependent effects of oral administration of CBD:TMP (5 mg/kg, 10 mg/kg, 15 mg/kg) compared to CBD (10 mg/kg) on anxiety, depression, social, and cognition behaviours in adult male Sprague Dawley rats following a 2-week chronic unpredictable stress protocol. We then ran molecular analyses of anxiety and depression biomarkers, along with whole brain and blood plasma concentration analyses of CBD, TMP, and their respective metabolites. Further, we performed pharmacokinetic studies to analyze the bioavailability of CBD:TMP (10 mg/kg) vs. CBD (10 mg/kg) in male Beagle dogs. In our behaviour studies, we report that CBD:TMP induced anxiolytic effects and reversed the behavioural effects of chronic stress such that animals that received CBD:TMP demonstrated reduced anhedonia, reduced learned helplessness, and increased pro-social behaviour - all of which are associated with an anti-depressant drug phenotype. In all cases, CBD:TMP significantly out-performed CBD. In our pharmacokinetic studies, we found the mean value for $C_{max}$/Dose of CBD was increased and that CBD and its metabolites showed enhanced levels after oral administration of CBD:TMP compared to CBD alone in a fasted state. Altogether, these results suggest the cocrystal CBD:TMP improves the efficacy and bioavailability of CBD. Overall, this research supports the development of CBD:TMP as a promising and superior alternative to CBD in the pharmacotherapeutic treatment of anxiety and depressive symptoms and phenotypes.

**Disclosures:** **M. Jones:** None. **T.C. Uzuneser:** None. **S. O'Sullivan:** A. Employment/Salary (full or part-time); Artelo Biosciences. **M. Sarikahya:** None. **A. Yates:** A. Employment/Salary (full or part-time); Artelo Biosciences. **W.J. Rushlow:** None. **S.R. Laviolette:** None.

**Poster**

**PSTR044. Preclinical Models of Anxiety**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR044.16/MM3

**Topic:** G.06. Anxiety Disorders

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One Mind – COMPASS Rising Star Award
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**Title:** Ventral hippocampal parvalbumin interneurons gate the anxiolytic action of the serotonergic psychedelic DOI

**Authors: *P. TIWARI**[1,2], P. DAVOUDIAN[3], D. KAPRI[2], A. BALAKRISHNAN[2], A. PRADHAN[2], A. C. KWAN[4], V. A. VAIDYA[2];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Tata Inst. of Fundamental Res., Mumbai, India; [3]Yale Univ. Sch. of Med., New Haven, CT; [4]Cornell Univ., Cornell Univ., Ithaca, NY

**Abstract:** There has been a recent renewal of interest in the therapeutic potential of serotonergic psychedelics for the treatment of mood-related disorders. Here, we uncover the essential role of ventral hippocampal GABAergic interneurons in the anxiolytic effect evoked by the serotonergic psychedelic 2,5-dimethoxy-4-iodoamphetamine (DOI). Integrating anatomical, pharmacological, and genetic approaches, we show that 5-$HT_{2A}$ receptors in the CA1/subiculum region of the ventral hippocampus are required for the anxiolytic action of DOI in mice and rats. *In vivo* electrophysiology indicates that DOI enhances the firing rate of hippocampal fast-spiking cells. Notably, restoration of 5-$HT_{2A}$ receptors in parvalbumin (PV)-positive inhibitory interneurons in a loss-of-function background reinstated the anxiolytic responses evoked by DOI in the vHpc CA1/sub region. Collectively, our results localize the anxiolytic action of a serotonergic psychedelic to 5-$HT_{2A}$ receptors in the ventral hippocampus, and specifically identify parvalbumin-positive fast-spiking cells as a cellular trigger for the psychedelic-induced relief of anxiety-like behavior.

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**Poster**

**PSTR044. Preclinical Models of Anxiety**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR044.17/MM4

**Topic:** G.06. Anxiety Disorders

**Title:** Effects of sudden removal of high social enrichment environment (such as that experienced during the COVID-19 pandemic) upon dopamine, norepinephrine, and serotonin neurotransmitter levels in structures of cortico-basal ganglia-thalamic circuits of the postmortem rat brain

**Authors:** H. B. ROBSON[1], S. M. FEEHAN[1], R. C. LICHTENSTEIN[1], ***D. S. KREISS**[2,1];
[1]First-Year Res. Immersion Program (Neuroscience), Binghamton Univ., Binghamton, NY;
[2]First-Year Res. Immersion Program (Neuroscience), Binghamton University, Dept. of Psychology, Binghamton, NY

**Abstract:** Removal of social enrichment can induce stress & exacerbate underlying psychiatric disorders. The goal of this study was to evaluate a novel stress-induced animal model in adolescent male (n=28) and female Sprague-Dawley rats (n=28). Stress was induced by suddenly transitioning Experimental rats to 4 weeks of standard enrichment (Day 77-106) following 5 weeks of high social enrichment (Day 34-76). Control rats experienced high social enrichment throughout. High social enrichment included housing in large cages with multiple toys, frequent handling, and 4 weekly “playdates” with 12 same sex non-cagemates. High Performance Liquid Chromatography was used to evaluate dopamine, norepinephrine, and serotonin levels in post-mortem tissue from targeted areas of cortico-basal ganglia-thalamic circuits (prefrontal cortex, motor cortex, anterior cingulate cortex, orbitofrontal cortex, amygdala, hypothalamus, dorsal hippocampus, lateral thalamus, medial thalamus, dorsal striatum, and ventral striatum). Removal of enrichment decreased monoamines in the prefrontal cortex, motor cortex, and lateral thalamus of both sexes. Sex was found to influence the effects of removal of enrichment. In the anterior cingulate cortex, serotonin in males increased, but decreased in females. In the hypothalamus, norepinephrine in males increased, but decreased in females. In the dorsal striatum, norepinephrine in males increased, but decreased in females. The table below summarizes change in neurotransmitter levels of Experimental rats versus Control rats. Better understanding of the neurophysiological consequences of a sudden removal of social enrichment (such as experienced during the COVID pandemic) has important translational value for treatment of psychiatric disorders.

| Change in Neurotransmitter Levels of Experimental versus Control Rats | | | | | | |
|---|---|---|---|---|---|---|
| Monoamines | NE | | DA | | 5-HT | |
| Sex | M | F | M | F | M | F |
| Prefrontal Cortex | ↓ | | | ↓ | | ↓ |
| Motor Cortex | ↓ | ↓ | ↓ | | ↓ | ↓ |
| Orbitofrontal Cortex | ↓ | | ↓ | | ↓ | |
| Anterior Cingulate Cortex | | | | | ↑ | ↓ |
| Lateral Thalamus | ↓ | ↓ | | ↓ | | |
| Medial Thalamus | | | ↓ | | ↓ | |
| Hypothalamus | ↑ | ↓ | | | ↓ | |
| Dorsal Striatum | ↑ | ↓ | ↑ | | ↑ | ↓ |
| Ventral Striatum | | ↓ | | | | ↓ |
| Hippocampus | | ↓ | ↓ | | x | x |
| Amygdala | | | | ↓ | | |

White arrows indicate increase ($p < 0.05$), black arrows indicate decrease ($p < 0.05$), grey arrows indicate trends ($0.05 > p < 0.08$), "x" = not measurable

**Disclosures:** **H.B. Robson:** None. **S.M. Feehan:** None. **R.C. Lichtenstein:** None. **D.S. Kreiss:** None.

**Poster**

**PSTR044. Preclinical Models of Anxiety**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR044.18/MM5

**Topic:** G.06. Anxiety Disorders

**Title:** Identifying a neural mechanism involved in predator induced anxiety

**Authors: *W. SMITH**[1,2], M. FRANCIS[2], A. KOEHLER[2], E. AZEVEDO[2];
[1]Delaware State Univ. Dept. of Biol. Sci., Dover, DE; [2]Neurosci., Med. Univ. of South Carolina, Charleston, SC

**Abstract:** Anxiety is a psychological and behavioral state where a threat to survival is perceived. Although this state is an adaptive function, it can transition to a pathological state if stress conditions become chronic. This results in maladaptive behaviors and contributes to the pathogenesis of anxiety disorders such as post-traumatic stress disorder and obsessive compulsive-disorders. However, how chronic exposure to threats can rewire brain circuits and contribute to anxiety is unclear. Recent evidence identified that stress and anxiety may have overlapping molecular and circuit mechanisms. In this study, we use predator odors to study the

neural mechanisms involved in stress and anxiety. As a model of innate fear and chronic stress, we used the artificial predator odor 2,5-dihydro-2,4,5-trimethylthiazoline (TMT) which was previously described to activate neural circuits that are associated with maladaptive behaviors. To determine how chronic stress induced by predator odor could affect anxiety-like behavior, we exposed male mice to 5 µl of undiluted TMT for 1, 7, 15 or 30 days or water as the odorless control. The behavioral consequences of predator odor exposure were assessed with Elevated Plus Maze and Novelty Suppress Feeding behavioral tasks. We found that mice exposed to TMT for 15 and 30 days showed significant increase in the latency to feed, in the time spent in the closed arms and a decrease in time spent in the open arms compared to the controls. However, mice exposed to TMT for 1 and 7 days showed no behavioral differences when compared to controls. Using c-fos mapping to determine which brain regions are important in inducing these effects, we found that the lateral septum was among the brain regions with the highest c-fos expression after TMT exposure. Our results demonstrate that chronic TMT exposure elicits a time-dependent increase in anxiety-like behavior, suggesting that a specific circuit rewiring mechanism may be critical for these changes. Our data also suggest that this rewiring may occur within the lateral septum. Overall, our study serves as framework to study the neural basis of anxiety and to understand the underpinnings of neuropsychiatric stress disorders.

**Disclosures:** **W. Smith:** None. **M. Francis:** None. **A. Koehler:** None. **E. Azevedo:** None.

**Poster**

**PSTR044. Preclinical Models of Anxiety**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR044.19/MM6

**Topic:** G.06. Anxiety Disorders

**Support:** NIH Grant AA027544
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University of Minnesota Doctoral Dissertation Fellowship

**Title:** Hyperexcitability of VTA GABA neurons mediates shock-stress induced anxiety-like behaviors in mice

**Authors: *E. H. MITTEN**[1], E. MARRON FERNANDEZ DE VELASCO[2], K. D. WICKMAN[2]; [1]Neurosci., [2]Pharmacol., Univ. of Minnesota, Minneapolis, MN

**Abstract:** The ventral tegmental area (VTA), which is commonly associated with reward processing, has recently been shown to be important for aversion processing and experiences plasticity following stress exposure. VTA gamma aminobutyric acid (GABA) releasing neurons are well-poised to be involved in the effects of stress due to several lines of evidence: (1) VTA GABA neurons make dense reciprocal projections to areas associated with fear, anxiety, and aversion, (2) VTA GABA Ca2+ activity tracks aversive and negatively valenced stimuli in both

Pavlovian and operant conditioning contexts, (3) optogenetic activation of VTA GABA neurons can induce fear responses, and (4) chemogenetic inhibition of VTA GABA neurons induces an anxiolytic and antidepressant phenotype. Recent evidence has shown that the expression of restraint stress-induced anhedonia is produced by aberrant activity of VTA GABA neurons. Therefore, we were interested in exploring if VTA GABA neuron activity can influence anxiety-like symptoms induced by stress and if these effects are generalizable to other forms of stress. Male and female C57BL/6J, GAD67-eGFP, and GAD-Cre mice (7-10 wk) were used for these experiments. We used a shock stress protocol consisting of a 20-min session with exposure to 20 electric foot shocks randomly interspaced at 30, 60, or 90 s. Control animals were exposed to the same chamber but did not experience foot shocks. The potential impact of sex in subsequent experiments was assessed utilizing a 2-way ANOVA. If no interaction was identified, data were pooled and analyzed via a Student's t-test or Mann-Whitney test, where appropriate. The shock stress protocol produced a significant anxiogenic phenotype in the light/dark box (LD) test 24 h after exposure ($t = 5.397$; $p < 0.0001$; $n = 12$-$13$). One day following shock stress, VTA GABA neurons in acutely isolated midbrain slices were hyperexcitable, as seen through an increase in the membrane resistance ($t = 2.775$, $p = 0.0089$), increase in baseline firing rate ($U = 100$, $p = 0.0030$) and decrease in rheobase ($U = 91.50$, $p = 0.0012$; $n = 20$-$21$). Furthermore, chemogenetic excitation of VTA GABA neurons in shock-stress naïve animals is sufficient to produce an anxiogenic phenotype in the LD test ($t = 4.018$, $p = 0.0008$, $n = 11$-$13$). Finally, preliminary data indicate that chemogenetic inhibition of VTA GABA neurons ameliorates anxiety-like behavior in the LD test induced by shock stress. In ongoing efforts, we are elucidating mechanisms underlying hyperexcitability evoked by shock stress, extending assessment of stress-induced plasticity of VTA GABA neurons to in vivo contexts, and evaluating other anxiety-like behaviors.

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**Poster**

**PSTR044. Preclinical Models of Anxiety**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR044.20/MM7

**Topic:** G.06. Anxiety Disorders

**Support:** CONAHCYT-226454
CONAHCYT-256448

**Title:** Quantitative EEG profile of the anxiolytic-like effects of palmitone in comparison to clinical drugs diazepam and buspirone in mice

**Authors: *D. MARTINEZ-VARGAS**[1], M. E. GONZÁLEZ-TRUJANO[2], D. ONOFRE-CAMPOS[1], F. G. MORENO-PÉREZ[2], F. NARVÁEZ-GONZÁLEZ[3], J. D. GONZÁLEZ-GÓMEZ[1], B. VILLASANA-SALAZAR[1];

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**Abstract:** Anxiety is a mental disorder with a growing worldwide incidence due to the SARS-CoV-2 pandemic. Pharmacological therapy includes drugs such as benzodiazepines (BDZs) or azapirones like buspirone (BUSP) or analogs, which unfortunately produce severe adverse effects or no immediate response, respectively. Medicinal plants or their bioactive metabolites are a shared global alternative to treat anxiety. Palmitone is one active compound isolated from *Annona* species due to its tranquilizing activity. However, its influence on neural activity and possible mechanism of action are unknown. In this study, an electroencephalographic (EEG) spectral power analysis was used to corroborate its depressant activity in comparison with the anxiolytic-like effects of reference drugs such as diazepam (DZP, 1 mg/kg) and BUSP (4 mg/kg) or 8-OH-DPAT (1 mg/kg), alone or in the presence of the $GABA_A$ (picrotoxin, PTX, 1 mg/kg) or serotonin 5-$HT_{1A}$ receptor antagonists (WAY100634, WAY, 1 mg/kg). The anxiolytic-like activity was assayed using the behavioral response of mice employing open-field, hole-board, and plus-maze tests. EEG activity was registered in both the frontal and parietal cortex, performing a 10 min baseline and 30 min recording after the treatments. As a result, anxiety-like behavior was significantly decreased in mice administered with palmitone, DZP, BUSP, or 8-OH-DPAT. The effect of palmitone was equivalent to that produced by 5-$HT_{1A}$ receptor agonists but 50% less effective than DZP. The presence of PTX and WAY prevented the anxiolytic-like response of DZP and 8-OH-DPAT, respectively. Whereas only the antagonist of the 5-$HT_{1A}$ receptor (WAY) inhibited the palmitone effects. Palmitone and BUSP exhibited similar changes in the relative power bands after the spectral power analysis. This response was different to the changes induced by DZP. In conclusion, brain electrical activity was associated with the anxiolytic-like effects of palmitone implying a serotoninergic rather than a GABAergic mechanism of action.

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**Poster**

**PSTR044. Preclinical Models of Anxiety**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR044.21/MM8

**Topic:** G.06. Anxiety Disorders

**Support:** UIC Graduate College Pathway to an Inclusive Faculty Fellowship
NIH Graduate Partnership Program

**Title:** Opioid receptor antagonism modulates the anxiolytic-like effect of oxytocin in mice

**Authors: *K. E. NISBETT**[1,3], *K. NISBETT[4], L. F. VENDRUSCOLO[2], G. F. KOOB[1];
[1]Neurobio. of Addiction Section, [2]Stress and Addiction Neurosci. Unit, Natl. Inst. on Drug Abuse, Baltimore, MD; [3]Grad. Program in Neurosci., Univ. of Illinois Chicago, Baltimore, MD; [4]Neurobio. of Addiction Section, NIH/NIDA, Baltimore, MD

**Abstract:** Anxiety disorders are leading causes of disability worldwide and are major contributors to substance use disorders (SUDs). Together, these disorder affect ~16% of the population and disproportionately affect men and women. A previous study by our laboratory demonstrated that intracerebroventricular (ICV) administration of oxytocin (500 ng) reduced anxiety-like behavior in male and female mice, with increased efficacy in males. Additionally, others have shown that mu opioid receptor (MOR) activation can reduce anxiety-like behavior and early studies suggest that the opioid receptors regulate the oxytocin system in relation to stress responses. Thus, we hypothesized that modulation of the opioid system mediates the sex differences observed in response to oxytocin treatment. To determine whether endogenous opioids mediated the effects of oxytocin, we systemically administered an opioid receptor antagonist, naloxone (1-4 mg/kg), prior to an effective dose of oxytocin (500 ng; ICV) in both males and females. Contrary to our initial hypothesis, our studies demonstrated that naloxone potentiated the anxiolytic-like effect of oxytocin. Using a MOR-selective antagonist, CTAP, and a kappa opioid receptor-selective antagonist, norbinaltorphimine, we demonstrated that MOR blockade potentiated the anxiolytic-like effect of oxytocin, whereas kappa-opioid receptor blockade inhibited oxytocin-induced anxiolytic-like effects. Our findings indicate that blockade of the opioid system may eliminate observed sex differences in the anxiolytic-like effects of oxytocin. Altogether these results suggest that endogenous opioids modulate the oxytocin system with respect to emotion regulation and have implications for the development of novel clinical treatments for anxiety disorders. As current clinical trials and treatment strategies include oxytocin or naltrexone (an opioid receptor antagonist), these findings have clinical implications for the prevention and treatment of SUDs that often arise because of self-medication in persons diagnosed with anxiety-disorders or contribute to emotional distress (hyperkatiefia) that can further exacerbate SUDs.

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**Poster**

**PSTR044. Preclinical Models of Anxiety**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR044.22/MM9

**Topic:** G.06. Anxiety Disorders

**Title:** A putative role of the neuroimmune system in heroin withdrawal

**Authors: *N. SAID**, H. MILLS, L. F. VENDRUSCOLO, G. F. KOOB;
NIH, Natl. Inst. on Drug Abuse (NIDA), Baltimore, MD

**Abstract:** Over the last two decades, opioid overdose has become the leading cause of accidental deaths in the United States, causing nearly 500,000 deaths from 1999 to 2019. Recent evidence suggests that glial activation and the related neuroimmune signals may be involved in the dependence-inducing properties of opioids. Although some treatments, like methadone buprenorphine naltrexone or naloxone, have proven effective, relapse rates remain high. Therefore, the identification of new non-opioid targets for the treatment of OUD is urgently needed. The main purpose of this study is to investigate the role of neuroimmune systems in opioid withdrawal-related behavior in rats. We first measured hyperalgesia and the aversive effects of heroin withdrawal in adult male (*n*=22) and female (*n*=23) Wistar rats. Hyperalgesia was assessed using the von Frey and Hargreaves tests, for mechanical and thermal sensitivity, respectively, after two weeks of repeated heroin administration. We also investigated the heroin withdrawal-induced conditioned place aversion (CPA) and naloxone-precipitated somatic withdrawal. Then, we quantified 17 cytokines and chemokines in whole brains of both saline- and heroin-treated rats by a FirePlex immunoassay. The data showed that two chemokines (CCL2 and CXCL1) and a cytokine (IL-10) were significantly upregulated in male rats that received heroin but not in females. Based on these results, we investigated whether an acute injection of a CCL2 antagonist could reverse the heroin-induced hyperalgesia, CPA and somatic withdrawal symptoms in heroin-dependent male (19) and female (20) Wistar rats. Results showed that the antagonist significantly reversed mechanical and thermal hyperalgesia, and attenuated CPA and somatic withdrawal symptoms in males and females. In summary, our findings suggest a sex-dependent proinflammatory effect of heroin withdrawal in the rat brain and that CCL2, CXCL1 and IL10 may be involved in the etiology of OUD. Our data also shows that CCL2 may contribute to motivational and somatic signs of opioid withdrawal in both male and female Wistar rats. Together, these investigations might lead the discovery of novel neuroimmune targets, such as chemokine antagonists, for opioid dependence and contribute to medication development for OUD.

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**Poster**

**PSTR044. Preclinical Models of Anxiety**

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**Topic:** G.06. Anxiety Disorders

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NIDA Intramural Research Program ZIA000069

**Title:** Dreadd-mediated amygdala activation induces anxiety-like responses in young nonhuman primates

**Authors: *P. H. ROSEBOOM**[1], S. A. L. MUELLER[1], J. A. OLER[1], N. AGGARWAL[1], M. M. KENWOOD[1], M. K. RIEDEL[1], V. R. ELAM[1], M. E. OLSEN[1], A. H. DIFILIPPO[2], B. T. CHRISTIAN[2], X. HU[3], A. GALVAN[3], M. MICHAELIDES[4], N. H. KALIN[1];
[1]Psychiatry, [2]Med. Physics, Univ. of Wisconsin Madison Sch. of Med. and Publ. Hlth., Madison, WI; [3]Emory Natl. Primate Res. Ctr., Emory Univ., Atlanta, GA; [4]NIH, Natl. Inst. on Drug Abuse Intramural Res. Program, Baltimore, MD

**Abstract:** Anxiety disorders are among the most prevalent psychiatric disorders, with symptoms often beginning early in life. To model the pathophysiology of human pathological anxiety, we utilized Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) in a nonhuman primate model of anxious temperament to selectively increase neuronal activity of the amygdala. Subjects included 10 young rhesus macaques; 5 received bilateral infusions of AAV5-hSyn-HA-hM3Dq into the dorsal amygdala, and 5 served as controls. Subjects underwent behavioral testing in the human intruder paradigm (HIP) following clozapine or vehicle administration, prior to and following surgery. Results of linear mixed effects (LME) analyses revealed a significant Group (hM3Dq vs. control) x Treatment (clozapine vs. vehicle) x Timepoint (pre- vs. post-surgery) interaction ($F_{1,376} = 4.22$, $p < 0.05$), such that, relative to vehicle, clozapine treatment led to relatively greater increases in freezing behavior during the post-surgical period across all contexts of the HIP in hM3Dq subjects and not in control subjects. Similarly, a significant Group x Treatment x Timepoint interaction was present for locomotion ($F_{1,376} = 15.25$, $p < 0.001$), such that, relative to vehicle, clozapine treatment led to relatively greater decreases in locomotion during the post-surgical period in hM3Dq subjects, while such decreases were not observed in control subjects. These results complement our previously published finding of a significant decrease in anxiety-like responses following DREADD-mediated inhibition of dorsal amygdala neurons. In the current study, similar effects on freezing ($F_{1,142} = 13.37$, $p < 0.001$) and locomotion ($F_{1,142} = 16.81$, $p < 0.001$) were again observed approximately 1.9 years following surgery, indicating the long-term functional capacity of DREADD-induced neuronal activation. Additionally, experiments performed at this time point with deschloroclozapine (DCZ), a clozapine analog with greater selectivity for DREADDs, also demonstrated similar effects on freezing ($F_{1,142} = 4.756$, $p < 0.05$). In DREADD expressing monkeys, [$^{11}$C]DCZ PET imaging demonstrated amygdala hM3Dq-HA binding, and immunohistochemistry revealed that hM3Dq-HA expression was most prominent in the neuropil of the basolateral amygdala. Electron microscopy demonstrated expression was predominantly on neuronal membranes. Together, these data demonstrate that activation of primate amygdala neurons is sufficient to induce increased anxiety-related behaviors, further supporting increased activity of the amygdala as a mechanism mediating pathological anxiety in humans.

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**Poster**

**PSTR044. Preclinical Models of Anxiety**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR044.24/MM11

**Topic:** G.06. Anxiety Disorders

**Support:** Sloan Fellowship

**Title:** Oxytocin neuromodulation of social isolation-induced anxiety in Tuberous Sclerosis Complex

**Authors: *P. SHRESTHA**[1,2], O. TABAKA[2], R. DEL RIO TRIANA[3], M. HOU[4], S. LAWAL[2], M. MARMARCZ[4], K. SAN AGUSTIN RUIZ[4], S. KIM[2], M. OLIVEIRA[4], J. E. LEDOUX[4], E. KLANN[3];
[1]Stony Brook, Smithtown, NY; [2]Neurobio. & Behavior, Stony Brook Univ., Stony Brook, NY; [4]Ctr. For Neural Sci., [3]NYU, New York, NY

**Abstract:** Stress is a major risk for the onset of several neuropsychiatric disorders including pathological anxiety. Social connection is a fundamental need for social animals including mice - it encompasses affiliative care, social play, vocal communication, and allogrooming among conspecifics. Prolonged involuntary isolation induces a sustained negative affective state that can precipitate maladaptive avoidance, a hallmark of pathological anxiety, in genetically susceptible individuals. Pathological anxiety is prevalent in up to 59% of patients with Tuberous Sclerosis complex (TSC), a neurodevelopmental disorder caused by loss-of-function mutations in genes for Tuberin (*Tsc2*) and/or Hamartin (*Tsc1*) that together comprise the eponymous protein complex. Anxiety in TSC patients can manifest as generalized anxiety in the form of excessive worrying, or can be episodic in the form of sudden, unexplained panic attacks. The neural circuit for stress has been extensively studied, and oxytocin (OT) signaling has been firmly established as a crucial component for moderating the outcome of stress response. The physiological effects of OT are mediated through its membrane-bound G-protein coupled receptors (OTRs) that are expressed in specific cells (OTRCs) distributed across the brain in state- and sex-dependent manner. OT is also well-known for its role in mediating behavioral and physiological responses to social exposure and for conferring social salience. In the absence of social environment, the OT's functional involvement in modulating the effects of stress is likely to be even more prominent. We hypothesized that selective disruption of TSC complex in OTRCs might cause heightened susceptibility to social isolation and precipitate maladaptive anxiety-related behaviors. On the basis of this hypothesis, we systematically carried out conditional knock out of an allele of *Tsc2* in OTRCs across the brain and body, and examined the effects of prolonged social isolation on anxiety-related behaviors in male and female mice. We further examined the restorative effects of administering drugs targeting distinct downstream effectors of TSC, and identified integrated stress response (ISR) as the molecular mechanism precipitating emotional susceptibility to social isolation in both sexes, albeit with striking sex differences in the indices of anxiety. Finally, we identified OTRCs in medial prefrontal cortex as the cellular loci that can be targeted for correcting behavioral phenotypes and electrophysiological signatures of aberrant network inhibition in male mice.

**Disclosures:** **P. Shrestha:** None. **O. Tabaka:** None. **R. del Rio Triana:** None. **M. Hou:** None. **S. Lawal:** None. **M. Marmarcz:** None. **K. San Agustin Ruiz:** None. **S. Kim:** None. **M. Oliveira:** None. **J.E. LeDoux:** None. **E. Klann:** None.

**Poster**

**PSTR044. Preclinical Models of Anxiety**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR044.25/MM12

**Topic:** G.06. Anxiety Disorders

**Title:** The effects of exercise, environmental enrichment and ketamine on behavior and gastrointestinal function in a mouse model of obsessive-compulsive disorder (OCD)

**Authors: *C. WILSON**, J. J. GATTUSO, A. J. HANNAN, T. RENOIR;
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**Abstract:** Background: Obsessive-compulsive disorder (OCD) is characterized by obsessions (i.e. intrusive thoughts) and compulsions (i.e. repetitive actions/mental rituals). OCD is frequently refractory to treatment and can have a profoundly deleterious effect on quality of life. While environmental interventions and novel rapid-acting antidepressants have been shown to be beneficial in the context of psychiatric disorders such as depression, such effects have not yet been comprehensively investigated in a preclinical model of OCD. Gastrointestinal function has also not been assessed preclinically, despite reports of gastrointestinal problems occurring in OCD. Given the lack of research in this area, we set out to conduct an exploratory investigation using a common preclinical mouse model of OCD-like behavior.
Methods: We used the SAPAP3 knockout (KO) mouse model, which displays an anxiety-like and over-grooming OCD-like phenotype. Female and male 8-wk-old SAPAP3 KO and wild-type (WT) mice were exposed to exercise or environmental enrichment (EE) (vs standard housing) for 4 weeks, followed by behavioral testing and assessment of gut function (n=7-12 (p/grp)). A second cohort of 10-wk-old SAPAP3 KO mice and WT control animals were administered a single dose of either saline (intraperitoneal injection, i.p.) or ketamine (an NMDAR antagonist; 30 mg/kg, i.p.) (n=13-17 (p/grp)). These mice underwent behavioral testing at baseline (i.e. before ketamine treatment) and at 1 hr, 24 hrs, 72 hrs, and 7 days after ketamine administration. Experimenters were blinded to genotype/treatment groups when scoring behavioral tests.
Results: SAPAP3 KO mice spent more time grooming than WT controls, an effect that was more pronounced in male KO animals. The KO mice also had a more ritualistic approach to grooming (i.e. an increased number of grooming chains), and showed increased anxiety-like behavior (on an approach-avoidance conflict test), decreased locomotion, and gut dysfunction. These impairments were not ameliorated following either environmental intervention, and paradoxically exercise worsened grooming behavior generally. In addition, we found that acute administration of ketamine did not cause a reduction in anxiety-like or grooming behavior.
Conclusion: Our study is the first to assess grooming microstructure and gut function in SAPAP3 KO mice, and is also the first to report a sexually dimorphic effect (accentuated in males) of

grooming in young-adult SAPAP3 KO mice. In addition, we found no beneficial effect of exercise, EE or the NMDAR antagonist ketamine in this model, and unexpectedly revealed a deleterious effect of exercise on some outcome measures.

**Disclosures: C. Wilson:** None. **J.J. Gattuso:** None. **A.J. Hannan:** None. **T. Renoir:** None.

**Poster**

**PSTR044. Preclinical Models of Anxiety**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR044.26/MM13

**Topic:** G.06. Anxiety Disorders

**Support:** Boehringer Ingelheim Fonds PhD fellowship
NIH grant R01DA014133
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**Title:** Dopaminoceptive D1 and D2 neurons in ventral hippocampus arbitrate approach and avoidance in anxiety

**Authors: *A. GODINO**[1], M. SALERY[1], A. M. MINIER-TORIBIO[1], V. PATEL[1,2], J. F. FULLARD[1,2], E. M. PARISE[1], F. J. MARTINEZ-RIVERA[1], C. MOREL[1,3], P. ROUSSOS[1,2], R. D. BLITZER[2,3], E. J. NESTLER[1,2];
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**Abstract:** The hippocampus, as well as dopamine circuits, coordinate decision-making in anxiety-eliciting situations. Yet, little is known about how dopamine modulates hippocampal representations of emotionally-salient stimuli to inform appropriate resolution of approach *versus* avoidance conflicts. We here study dopaminoceptive neurons in mouse ventral hippocampus (vHipp), molecularly distinguished by their expression of dopamine D1 or D2 receptors. We show that these neurons are transcriptionally distinct and topographically organized across vHipp subfields and cell types. In the ventral subiculum where they are enriched, both D1 and D2 neurons are recruited during anxiogenic exploration, yet with distinct profiles related to investigation and behavioral selection. In turn, they mediate opposite approach/avoidance responses, and are differentially modulated by dopaminergic transmission in that region. Together, these results suggest that vHipp dopamine dynamics gate exploratory behaviors under contextual uncertainty, implicating dopaminoception in the complex computation engaged in vHipp to govern emotional states.

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**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.01/MM14

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** T32 AA 007462

**Title:** Protracted Intake Increases Alcohol Engagement in the 5 Choice Serial Reaction Time Task

**Authors: *A. SIEGLE**[1], P. A. STARSKI[2], F. W. HOPF[3];
[1]Indiana University-Purdue Univ. Indianapolis, Indianapolis, IN; [3]Indiana Univ., [2]Indiana Univ. Sch. of Med., Indianapolis, IN

**Abstract:** Alcohol use disorder (AUD) is characterized by excessive drinking which can lead to a dependence on alcohol. Approximately 15 million Americans are affected, and more than 88,000 Americans die annually from alcohol related deaths. Those with AUD and higher rates of alcohol drinking are more likely to have health issues, such as liver problems, cognitive dysfunction, psychiatric disorders, and a more frequent rate of illness. Several factors contribute to the development and progression of AUD, including impulsivity, motivation, and attention. Previous studies have investigated these behavioral facets using the 5-Choice Serial Reaction Time Task (5-Choice) with a sugar-based reward. Recently, our lab published a study using alcohol as a reward and identified alcohol preference, as determined by a 2-bottle choice paradigm, as a predictor to 5-Choice performance for alcohol, not sugar. In the current study, we reapproached this data in a novel way that describes a stronger relation between groups of mice based on engagement. We recategorized 48 male C57BL/6 mice into high-engaged (HE) and low-engaged (LE) as determined by a median split of their average number of correct responses during the last week of training. Early- and Late-stage behavior showed a clear difference in overall standard performance measures. Interestingly, over half of HE mice had an alcohol preference greater than 80 percent while LE had only a third. Additionally, alcohol preference correlated average correct responding across Early- and Late-stage training in the HE mice, but not for LE. After training, these mice underwent two bottle choice intermittent access (IA2BC), where they received 20 percent alcohol three days per week for three weeks. Following IA2BC, LE mice significantly increased overall performance for the alcohol reward, while HE mice did not. In comparison to the preference and consumption analyses in the previous study, engagement presented a clearer description of individuals that will work for alcohol and suggests that low alcohol engaged individuals may be at greater risk of AUD development after protracted drinking.

**Disclosures: A. Siegle:** None. **P.A. Starski:** None. **F.W. Hopf:** None.

**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.02/MM15

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** K99/R00-AA025393

**Title:** Non-selective opioid receptor blockade does not alleviate alcohol-induced cognitive dysfunction

**Authors: *A. ASKINS**[1], M. ASOKAN[1], S. FLORESCO[2], L. NATIVIDAD[1];
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[2]Dept. of Psychology and Djavad Mowafaghian Ctr. for Brain Hlth., Univ. of British Columbia, Vancouver, BC, Canada

**Abstract:** Prolonged alcohol (EtOH) misuse is associated with neuroadaptations in the brain that influence the emergence of addiction behavior, including impairments in cognitive function. We and other laboratories have noted similar deficits in rats exposed to chronic intermittent EtOH (CIE) vapor and shown that these cognitive impairments are both long-lasting in abstinence and involve dysfunctions in cortical brain regions, such as the medial prefrontal cortex (mPFC). More recently, we employed a large-scale analysis of the mPFC proteome to reveal a deficiency in the phosphorylation of mu-type opioid receptors (MOR) of dependent rats displaying cognitive inflexibility. As deficits in phosphorylation may allude to mechanisms that modulate opioid receptor sensitivity, here we examined whether non-selective opioid receptor blockade using the therapeutic naltrexone (NTX) influenced EtOH-induced cognitive dysfunction. Male Long-Evans rats were first trained to lever press for food pellets in operant chambers, followed by CIE vapor exposure for 6 weeks (14h/daily; blood EtOH levels= 191.25±7.51 mg/dL). Dependent rats and their EtOH-naïve counterparts were then trained on an operant model of strategy set-shifting, beginning with a visual discrimination task in which levers were presented along with a cue light that signaled the reinforced lever. On day 10 of abstinence, rats were given a single dose of NTX (2 mg/kg, IP; n=14-15/group) and introduced to an automated sequence beginning with the “visual cue” rule, followed by a switch to the spatial location task, in which only one lever was reinforced. Overall, EtOH dependence was associated with an increase in the total errors committed when switched over to the spatial location task ($p<0.05$), and this effect was undifferentiated from their NTX-treated counterparts. Interestingly, the total omissions committed after the switch also increased unanimously in NTX-treated rats ($p<0.01$), although these increases tended to be higher in naïve vs. dependent rats ($p=0.064$). The findings suggest that dependence is associated with prolonged desensitization of MOR in the mPFC, and diminished pharmacological influence on some aspects of cognitive performance. While clearly shown in the clinic to reduce high-level EtOH consumption, it is not clear whether therapeutics like NTX address other hallmark symptoms of alcohol use disorder (e.g., cognitive dysfunction). Current studies are evaluating the possibility that CIE exposure impairs intracellular kinases known to phosphorylate MOR and promote receptor desensitization.

**Disclosures:** **A. Askins:** None. **M. Asokan:** None. **S. Floresco:** None. **L. Natividad:** None.

**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.03/MM16

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** NIH Grant (AA027773)

**Title:** Repeated ethanol exposures alter the reward-dependent spatiotemporal cellular activities in the dorsal striatum

**Authors:** ***A. BENNETT**, H. KIM, P. BIGGS, S. KANG;
Med. Col. of Georgia at Augusta Univ., Augusta, GA

**Abstract:** The dorsal striatum (DS) has been known to shape context-dependent decision-making. In the DS, the direct- and indirect-pathway medium spiny neurons (dMSNs and iMSNs) orchestrate and yield biased behavior in reward-seeking exploratory tasks according to the existence of approach and avoidance conflict. Accumulative evidence suggests that the anterior and posterior DS subregions have distinctive roles in context-dependent reward-seeking behaviors. However, little is known about how the coordinated activities of the neurons in the DS subregions encode the specific responses to different rewards. In addition, it is still elusive whether repeated ethanol exposure affects this coordination.Using multi-regional fiber-photometry calcium imaging, we examined the spatiotemporal activities of the neurons in the dorsomedial striatum (DMS) and tail of striatum (TS) simultaneously in a three-arm reward choice task that consists of the modified y-maze arena for unconstrained access to water, sucrose (15%, w/v), and ethanol (15%, v/v) solutions for 10 minutes. A fluorescent calcium sensor, GCaMP6, was selectively expressed in dMSN and iMSNs of transgenic mice expressing both Cre-dependent GCamP6s and D1R-Cre or D2R-Cre. We compared whether the cellular profiles could be affected by the exposure to chronic intermittent ethanol (CIE) paradigm. Briefly, mice were exposed to air or vapored ethanol in vapor inhalation chamber for four weeks. Each week consisted of four consecutive days of ethanol exposure for 16h followed by 8h of abstinence in their home cage. The remaining 3 days consisted of no exposure to ethanol.We observed that, in the ethanol-naïve mice, the time spent in the sucrose zone is significantly higher compared to the time in ethanol zone. Interestingly, at 72h withdrawal from the CIE exposure, mice showed the increased time spent in the ethanol zone without changes to the time spent in the sucrose zone compared to those of ethanol-naïve counterparts. In conjunction with these findings, while the ethanol-naïve mice showed a decrease in $Ca^{2+}$ transients of the dMSNs in the DMS when approaching the ethanol zone, the $Ca^{2+}$ transients in the CIE mice were robustly increased when approaching the ethanol zone. No significant changes were observed in the $Ca^{2+}$ transient patterns of the TS neurons as the mice approached the ethanol zone.Our results indicate that the dMSNs' activities in the DMS are responsive to ethanol, which could be oppositely increased

upon repeated ethanol exposures, suggesting that the neuronal activities represent reward-dependent behavioral flexibility and shape the progressive transition of the ethanol value as a reward.

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**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR045.04/MM17

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** NIGMS GM113131 Grant

**Title:** Behavioral Markers and Endophenotypes Underlying Individual Differences in Ethanol Use

**Authors: *A. KALINOWSKI**, H. MANNING, K. ALIMANDI, H. KNAPP, E. O'KEEFE, B. TOWER, M. DEANE, T. ALLEN, J. HENSLEY, S. CHARNTIKOV;
Univ. of New Hampshire, Durham, New Hampshire, NH

**Abstract: Behavioral Markers and Endophenotypes Underlying Individual Differences in Ethanol Use**Anna Kalinowski, Hannah Manning, Kelsey Alimandi, Ethan O'Keefe, Haily Knapp, Blake Tower, Megan Deane, Sergios CharntikovAlcohol Use Disorder (AUD) is a chronic disease with a high relapse rate, affecting a substantial proportion of the global population. This disorder represents the third leading cause of death, contributing to approximately 3 million fatalities per year. Despite abundant research on ethanol use in preclinical settings, individual effects associated with ethanol use remain largely unexplored. This study seeks to assess the various individual effects along the ethanol use continuum. The primary aim is to ascertain if rats exhibiting a higher preference for ethanol, quantified by their "economic" demand, also show increased ethanol self-administration despite negative consequences and show high rates of relapse during cue-induced reinstatement of ethanol seeking. A concurrent study will investigate the neural substrates involved in cue-induced reinstatement, utilizing both group and individual levels of assessment. In this study, twelve female and twelve male rats were trained in operant chambers to self-administer ethanol using a long-access self-administration model (10 hours). Subsequently, the rats were individually assessed for their economic demand for ethanol and their responses to ethanol in the presence of negative consequences (a mild electric shock). Following this, the rats underwent extinction training and cue-induced reinstatement. For the first time, we demonstrate that individual variability in economic demand for ethanol can predict relevant behaviors within the substance use cycle. Specifically, our results indicate that rats with a high demand for ethanol persist in responding to ethanol despite negative consequences and show a vulnerability to cue-induced reinstatement. Our ongoing research aims to leverage this individual variability to examine the

neural substrates involved in cue-induced ethanol seeking, potentially offering novel targets for future studies. Further research focusing on individual variations in ethanol consumption is crucial to validate our findings. Such investigative efforts could greatly enhance our understanding of the complex behavioral and neural mechanisms that underpin ethanol use.

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**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.05/MM18

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** AA028145

**Title:** Sex differences in the effect of alcohol withdrawal on sleep and circadian rhythms

**Authors: *A. ALTAMIRANO**[1,2], C. FORBES[1,2], R. GUO[2], Y. HUANG[2], M. M. TORREGROSSA[2];
[2]Psychiatry, [1]Univ. of Pittsburgh, Pittsburgh, PA

**Abstract:** Sex differences in the effect of alcohol withdrawal on sleep and circadian rhythmsAuthors: Alain Altamirano-Espinoza, Rong Guo, Camryn Forbes, Yanhua Huang, Mary M Torregrossa. Affiliation: Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, United States.
Alcohol is the most widely available substance of abuse world-wide. The brain systems and neurotransmitters orchestrating the sleep-wake cycle are highly susceptible to the pharmacological properties of alcohol. Consequently, alcohol is commonly used as a sleep aid, and this can lead to alcohol misuse. Further, abstinence from alcohol use in heavy drinkers or those with alcohol use disorder (AUD) is associated with chronic changes in sleep quality, including increased REM sleep pressure, that is associated with relapse propensity within 6 months. However, individual differences in REM sleep quality and sleep homeostasis during withdrawal, particularly with regard to sex differences, have not been fully examined. Thus, in these studies, we used male and female (n=11 and n=12, respectively) EEG/EMG-implanted Long Evans rats to determine baseline measures of sleep quality immediately prior to alcohol intake and in withdrawal (21 days) from 3 weeks of intermittent access two-bottle choice (IA2BC) alcohol (20% v/v) drinking. **Results**. As previously reported by our lab and others, female rats drank significantly more alcohol in g/kg relative to male rats. Sleep files were then scored using Somnivore software to identify different sleep/wake states (wake, non-rapid eye movement [NREM] sleep, and REM sleep). In females, we found no significant differences in the time rats spent in any sleep/wake state. In contrast, there was a shift in the time male rats

spent in all states and phases (except dark phase REM). Moreover, we found differences in light-dark transitions to all states in female rats, indicating a change in circadian rhythms that was not as apparent in male rats. Finally, bout analysis showed differences in the number of bouts of REM sleep during the light phase selectively in males. These results suggest that alcohol exposure induced changes in one or more brain regions regulating sleep and circadian rhythms in the brain, (e.g. suprechiasmatic nucleus, habenula, etc.), with differential effects in males and females. In conclusion, our results suggest that alcohol intake differentially shapes specific aspects of the sleep-wake cycle in male and female rats, while more studies are required to identify the underlying mechanisms for such differences.

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**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.06/MM19

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** 5R00AA028298-04

**Title:** Social dominance predicts ethanol preference in socially housed mice

**Authors: *C. JOHNSTON**, A. MEYERS, M. PINA;
Anat. and Neurobio., Univ. of Maryland Baltimore, Baltimore, MD

**Abstract:** Social dominance plays an important role in the generation of motivated behaviors. Dominance has specifically been shown to play a role in motivation toward ethanol consumption. However, many of these experiments focused on dyads, examining the relationship between one dominant and one submissive subject. In the present study, we focus on mischiefs of 4 mice, as it represents a more ethologically valid setting. We hypothesized that ethanol consumption would be predicted by social rank, and that this effect would be independent of anxiety/exploration. Male and female C57BL/6J mice were housed in same-sex groups of 4 (8 males and 8 females) and put through the open field test (OFT), 4 days of the social dominance tube test (SDTT), and one cycle of a two-bottle choice drinking in the dark (DiD) paradigm. After drinking, mice were put through another 4 days of the SDTT and OFT. We found that one week of DiD did not significantly affect social rank. Social rank predicted ethanol preference on the first day and trended toward predicting ethanol preference on the fourth and final day of ethanol exposure, such that the higher ranked a mouse, the more likely they were to prefer ethanol. Social rank also related to exploratory behavior in a sex-specific manner: males of a higher social rank explored more of the OFT, while females of a higher social rank trended toward exploring less of the OFT. Furthermore, within sex and within a cage, the weight of a mouse had no effect on that mouse's social dominance score. This work expands on previous

literature examining how motivation is affected by social rank. The opposite relationship of social dominance and exploration between sexes also bears future investigation. Future work should also explore the shared neurobiological underpinnings of social rank and alcohol consumption. Furthermore, the possibility of the relationship between social dominance and ethanol preference changing with repeated weeks of the DiD paradigm should be investigated. Such a result could disentangle whether the observed ethanol preference is a product of either novelty preference or genuine ethanol preference. The overarching goal of this work is to establish a predictive index of social traits that suggest an increased propensity to consume alcohol and risk for developing an alcohol use disorder.

**Disclosures:** **C. Johnston:** None. **A. Meyers:** None. **M. Pina:** None.

**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.07/MM20

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** NIAAA Grant K01-AA027833

**Title:** Chronic health conditions and substance use disorders in patients meeting criteria for alcohol use disorders

**Authors: *K. JANIUK**, N. MALEKI;
Massachusetts Gen. Hosp., Charlestown, MA

**Abstract:** Through December 2021 to late July 2022, we evaluated 62 (24 Men, Age: 51.2 (mean) ± 10.9 (std)) patients who met the criteria for Alcohol Use Disorders (AUD). The participants were selected from a pool of patients of the Massachusetts General Brigham hospitals that were billed for an ICD-10 code for AUD with and without Pain. We evaluated the patients using a series of questions on their health history, medical care, as well as any other substance use. Our results showed that in this population, at any given point in time whether it be current or past substance use, 82% of patients who met the criteria for AUD also use or had a history of using some kind of substance. We also found that the conditions that impacted 50% or more of the population surveyed were: High Blood Pressure (52%), Pain (55%), Sleep Problems (60%), and Psychiatric Disorders (73%). Some patients were selected based on also having an ICD-10 code for pain, which may explain finding pain among the conditions. We also found that the percentage of patients with certain self-identified conditions was significantly different from the percentage of patients who had received a formal diagnosis and treatment for such conditions. Less than 50% match was noted for Major Head Injury/TBI (48%), Dizziness or Vertigo (48%), Cognitive/Memory Problems (43%), and Fainting Spells/Blackouts (29%). The severity of the diagnoses and the mismatch between the medical care received, suggests that this

patient population has complex healthcare needs that are not being adequately addressed for unknown reasons.

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**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

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**Program #/Poster #:** PSTR045.08/MM21

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** 5R01DA043461-05

**Title:** Examining the effects of alcohol and social isolation on the reinforcing properties of ketamine and dendritic spine morphology in the nucleus accumbens of male and female rats

**Authors: *S. D. JENNINGS**, M. KABBAJ;
Biomed. Sci., Florida State Univ., Tallahassee, FL

**Abstract: Rationale:** While preclinical and clinical research shows that ketamine, an NMDA receptor antagonist, is efficacious in treating depression, studies have not considered comorbidity between depression and alcohol use disorders (AUD) or the safety of repeated infusions of ketamine in depressed alcoholic patients. Given alcohol and ketamine's overlapping mechanisms of action, it is important to consider how alcohol may influence the reinforcing effects of repeated ketamine treatment. **Objective:** To determine in male and female rats whether a history of chronic social isolation and alcohol alter the reinforcing properties of ketamine. **Methods:** For 12 weeks, adult male and female pair-housed or socially isolated rats intermittently drank alcohol (20%) or water. Subsequently, rats underwent acquisition of intravenous ketamine self-administration (0.5 mg/kg/infusion) under a fixed ratio schedule 1, followed by extinction training, and one session of cue-induced reinstatement, after which rats were terminated and their nucleus accumbens were processed for examination of dendritic spine morphology using a diolistic labeling approach. **Results:** Our results suggest that 1) During acquisition, female rats self-administer more ketamine than male rats; 2) A history of alcohol increases responding for ketamine during acquisition phase in both sexes, regardless of housing, 3) Isolation stress increases the reinforcing properties of ketamine in male but not female rats, 4) All experimental groups extinguished similarly and there were no clear differences in reinstatement between ketamine and saline exposed rats. **Conclusions:** Overall, our data show that a history of alcohol increases the reinforcing properties of ketamine and thus suggest that ketamine doses used for treating depressed patients with comorbid AUD can be lowered. We are currently analyzing dendritic spines in the nucleus accumbens to determine whether these changes can represent a neurobiological basis for interactions between alcohol and ketamine.

**Disclosures: S.D. Jennings:** None.

**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.09/MM22

**Topic:** G.09. Drugs of Abuse and Addiction

**Title:** Beta-endorphin reduces ethanol-induced sedation and ataxia in mice

**Authors: S. G. STEA**, *J. GRISEL;
Bucknell Univ., Lewisburg, PA

**Abstract:** Beta Endorphin (β-E) is an opioid peptide that has been linked to the behavioral effects of ethanol (EtOH). For example, β-E provides negative feedback to inhibit the hypothalamic-pituitary-adrenal (HPA) stress axis, and neuroadaptation of this system to EtOH may facilitate sex differences in disordered drinking. Locomotor sensitivity to EtOH also may influence the risk for addiction, however the role of β-E in psychomotor effects of EtOH is not fully understood. We examined the influence of β-E and sex on locomotor effects of EtOH using adult male and female wild-type C57BL/6J and β-E deficient B6.129S2-Pomctm1Low/J mice in a parallel rod floor apparatus following 0.75 or 2.0g/kg EtOH. Beginning 15 min after intraperitoneal injection, we recorded foot slips, distance traveled, slips per meter, first instance of immobility and total time spent off-balance (lying on the floor) for 15 min, and collected blood for analysis of EtOH concentration 60 min after injection. Overall, β-E deficient mice were more sedated and ataxic following EtOH; at the lower dose they slipped more frequently and had a higher rate of slips per meter traveled. At the higher dose, β-E deficient mice were predominantly sedated, slipping less frequently and traveling less, as well as spending more time off-balance and becoming immobile sooner. Genotype interacted with sex in that male β-E deficient mice had the greatest slip count and slips per meter at the low dose, suggesting that the β-E may elicit sex dependent effects of EtOH induced ataxia. Blood EtOH concentration did not differ between any group, suggesting that behavioral differences result from altered sensitivity to EtOH. Our data support the contention that β-E modulates the locomotor effects of EtOH and may influence ataxia in a sex dependent manner. These findings help elucidate the role of β-E in diverging behavioral responses to EtOH and may aid the development of risk factor classification and targeted treatments for alcohol use disorders.

**Disclosures: S.G. Stea:** None. **J. Grisel:** None.

**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.10/MM23

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** NIH Grant R01 AA027660 (PN)

**Title:** Inhibition of the sodium-calcium exchanger reverse mode activity reduces alcohol consumption in rats.

**Authors:** G. K. R. S. CARDOSO, ***P. N'GOUEMO**;
Physiol. & Biophysics, Howard Univ. Col. of Med., Washington, DC

**Abstract:** Alcohol withdrawal seizures (AWSs) are severe neurological conditions associated with drinking. One specific target of alcohol in the brain is the sodium-calcium exchanger (NCX), which can function in a forward or reverse mode. The forward mode drives the extrusion of $Ca^{2+}$ and the entry of $Na^{+}$, while the reverse mode ($NCX_{rev}$) drives the entry of Ca2+ and the extrusion of $Na^{+}$. We have previously reported that suppressing $NCX_{rev}$ activity significantly reduces the incidence and severity of acoustically evoked AWSs, suggesting that $NCX_{rev}$ activity could play a role in alcohol consumption. Here, we investigated the potential role of NCX reverse mode activity type 1 ($NCX1_{rev}$) and 3 ($NCX3_{rev}$) in voluntary alcohol consumption in adult male and female Sprague-Dawley rats. SN-6 and KB-R7943 were used to block $NCX1_{rev}$ and $NCX3_{rev}$, respectively. Over four weeks, animals were first trained to drink ethanol (7.5% vol/vol in water) using the two-bottle choice paradigm, one with ethanol and the other with water. Animals were then randomly divided into eight groups (n=8), each consisting of male or female rats treated with either KB-R7943 (3 or 10 mg/kg, p.o.) or SN-6 (3 or 10 mg/kg, p.o.). We measured ethanol intake, ethanol preference, water intake, and total fluid intake per kilogram of body weight after 2 or 24 hours of access. We also monitored the estrous cycle to find that all females were in the estrus cycle. The results showed that inhibiting $NCX1_{rev}$ activity reduced alcohol consumption in both male and female rats, with a long-lasting effect observed in females. SN-6 also reduced alcohol preference in females but did not change water intake in either sex. Blocking $NCX3_{rev}$ activity only lowered alcohol consumption in female rats without altering water intake or alcohol preference. Our findings suggest that increased $NCX_{rev}$ activity may contribute to voluntary alcohol consumption.

**Disclosures: G.K.R.S. Cardoso:** None. **P. N'Gouemo:** None.

**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.11/MM24

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** NIH Grant P20GM130461

**Title:** Alcohol drinking in rats is differently modulated by the type of sugar added: regulation by melanin-concentrating hormone

**Authors: *I. R. K. KUEBLER**, G. ZIMMERMAN, S. Q. NG, H. SCHNEIDER, B. MATTES, K. SEXTRO, A. DENNING, G. HATCHER, M. MATUSZESKI, M. SUAREZ, K. T. WAKABAYASHI;
Psychology, Univ. of Nebraska, Lincoln, Lincoln, NE

**Abstract:** Sugars in alcoholic beverages increase palatability and facilitate intake, furthering the development of alcohol use disorder. Some added sugars like glucose can also directly impact brain activity. Melanin-concentrating hormone (MCH) neurons in the lateral hypothalamus (LH) are sensitive to glucose and regulate sugar and alcohol intake. This study seeks to establish drinking patterns of alcoholic cocktails containing either glucose or fructose and to determine the impact of MCH function in modifying intake of these cocktails. Adult female and male Wistar rats were intracranially infused with an adenovirus vector delivering an excitatory Designer Receptor Exclusively Activated by Designer Drugs (DREADD) targeting LH MCH neurons. Rats were trained to drink either 10% glucose or 10% fructose cocktails in four-hour sessions, five days per week. The dose of alcohol increased weekly (1.25%, 2.5%, 5%, 10%). Once trained, the alcohol dose varied weekly in a Latin square design. During test sessions, MCH neurons were activated by clozapine-*n*-oxide or vehicle. The systemic effects of the MCH receptor antagonist GW803430 or vehicle were also determined. Volume drank was estimated via optical lickometers and changes in bottle weight. Sugar type dose-dependently affected drinking for both female and male rats: glucose increased drinking, alcohol intake, and caloric intake compared to fructose at 1.25% and 2.5% alcohol, while fructose increased intake at 10% alcohol. In males, MCH receptor antagonism decreased alcohol intake of cocktails containing glucose or fructose at a moderate alcohol concentration. MCH neuronal activation decreased alcohol intake only at the highest alcohol concentration containing fructose. Sex differences will be detailed during the poster session. The LH MCH brain circuit may be an important mechanism for how sugars and alcohol influence patterns of intake and subsequent behavioral symptoms associated with alcohol use disorder.

**Disclosures: I.R.K. Kuebler:** None. **G. Zimmerman:** None. **S.Q. Ng:** None. **H. Schneider:** None. **B. Mattes:** None. **K. Sextro:** None. **A. Denning:** None. **G. Hatcher:** None. **M. Matuszeski:** None. **M. Suarez:** None. **K.T. Wakabayashi:** None.

**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.12/MM25

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** NIAAA, grant R01AA026820 to C.J.

**Title:** Exploration of Novel Chemotypes as GPR88 Agonists: Design, Synthesis, and SAR Studies of (4-Substituted-phenyl)acetamides Based on the Reversed Amide Strategy

**Authors: *M. RAHMAN**, D. GUAN, H. CHAMINDA LAKMAL, A. M. DECKER, D. L. HARRIS, C. JIN;
RTI Intl., RTP, NC

**Abstract:** Central Nervous System (CNS) disorders such as alcohol use disorder (AUD), schizophrenia, and Parkinson's disease (PD) remain mostly unmet which poses significant economic burden to the society. As a result, there is much interest in GPR88 as a potential drug target, which has been proven to play crucial roles in these psychiatric and neurodegenerative diseases. Although the endogenous ligand for GPR88 is yet to be discovered, extensive medicinal chemistry campaigns have uncovered highly potent and brain-penetrant agonists such as RTI-13951-33 and RTI-122. Although these agonists have been used as effective probes to study GPR88's functions in the brain, there is still need for further optimization. With the aim of further improving the pharmacotherapeutic properties, as well as gaining access to new chemical space, we have developed novel (4-substituted-phenyl)acetamides based agonists for GPR88 that arise from bioisosteric replacement of amide functionality of the 2-AMPP scaffold. The rational design, synthesis, SAR, and computational docking studies based on the recently elucidated *cryo*-EM structure of GPR88 will be presented.

**Disclosures: M. Rahman:** None. **D. Guan:** None. **H. Chaminda Lakmal:** None. **A.M. Decker:** None. **D.L. Harris:** None. **C. Jin:** None.

**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.13/NN1

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** Emmanuel College Faculty Startup Funding

**Title:** Environmental enrichment and isolation effects on anxiety-like and depression-like behavior and ethanol self-administration in male and female mice

**Authors: G. W. NOLAN**, S. M. MIRRIONE, T. R. HARRISON, *E. J. CROFTON;
Emmanuel Col., Boston, MA

**Abstract:** A small proportion of individuals that drink alcohol become dependent or develop alcohol use disorder. We are investigating this susceptibility versus resilience to addiction-related, anxiety-like, and depression-like behaviors using the animal model environmental enrichment. Enriched mice are group-housed in a large environment with several conspecifics and plastic objects that are regularly changed and rearranged while isolated mice are single housed in standard cages. Previous work has found that enriched rodents are resilient to anxiety-

like and addiction-related behaviors. Here we examined whether environmentally enriched mice compared to isolated mice showed alterations in anxiety-like, depression-like behavior, and ethanol self-administration. Male and female mice were housed in enriched or isolated conditions from weaning for a minimum of 30 days before behavioral testing including sucrose neophobia, sucrose preference, elevated plus maze, forced swim test, open field test, and ethanol self-administration. Environmental enrichment did not significantly alter body weights after differential rearing, although females had lower body weights compared to males. When exposed to a novel taste in the sucrose neophobia test, there were no differences in sucrose solution intake between enriched and isolated male and female mice after 30 minutes and 24 hours of exposure. Environmentally enriched females showed a trend towards a decrease in preference of a sucrose solution over water compared to isolated females with no changes in males. We also examined environmental enrichment versus isolation on ethanol self-administration using a two-bottle choice paradigm. Mice were given access to water and ethanol (20% v/v) for 24 hours on a M-W-F schedule for a total of 20 drinking days with free access to water on intervening days. Females overall drank more ethanol compared to males, however there was no effect of environmental enrichment or isolation. We also found a significant effect of ethanol drinking day over the intermittent access protocol, suggesting changes in intake over time in all groups. There were no significant main effects of sex or enrichment on water intake and preference for ethanol. Ongoing assessments will evaluate differences in anxiety-like behavior with elevated plus maze, depression-like behavior with forced swim test, and activity levels with open field testing. Overall these data suggest increases in anhedonia-like behavior in environmentally enriched females and show that female mice self-administer more ethanol compared to males, regardless of differential rearing environments.

**Disclosures: G.W. Nolan:** None. **S.M. Mirrione:** None. **T.R. Harrison:** None. **E.J. Crofton:** None.

**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.14/NN2

**Topic:** G.09. Drugs of Abuse and Addiction

**Title:** Sex differences in alcohol consumption posterior to naltrexone treatment in rats with low and high alcohol intake

**Authors: *I. E. ZAPEDOWSKA**[1], L. M. MOLINA-MARTÍNEZ[2,1], J. JUÁREZ[1];
[1]Inst. de Neurociencias CUCBA, [2]Dept. de Biología Celular y Molecular, CUCBA, Univ. de Guadalajara, Guadalajara, Mexico

**Abstract:** Naltrexone (opioid antagonist), is used to treat alcohol abuse. However, in experimental studies, there is evidence that alcohol consumption is increased after naltrexone treatment when it´s administered in a period of time without alcohol exposition. Apparently, this

phenomenon is due to opioid antagonists produce an up-regulation of *mu* opioid receptors after several days of treatment increasing the availability of this receptor and contributing to increased reinforcing effect of alcohol. Moreover, there are sex differences in alcohol consumption in rats, females tend to drink more alcohol in comparison with males. However, it is not known, at the present time, a possible different response to alcohol intake after naltrexone treatment in male and females. On this basis, forty male and female *Wistar* rats were exposed to alcohol at 10% to establish the base line during 8 days. Then, they were treated with naltrexone 1mg/kg or saline solution 1ml twice a day intragastrically for 6 days. Then, they were re-exposed to alcohol at 10% during 8 days. In the period posterior to the treatment, an enhancement in alcohol consumption was observed in all groups regardless of naltrexone treatment. Due to a high variability intragroup, the subjects were divided between high and low alcohol consumers during their base line. In females with low base line consumption, the enhancement didn´t occur after naltrexone treatment, while in those with high base line consumption, alcohol consumption was enhanced compared to control group. In males, the enhancement occurred in both, those with high and low base line consumption regardless of the treatment with naltrexone. These results, suggest that the enhancement of alcohol consumption after naltrexone treatment, depends on sex and on the level of base line consumption.

**Disclosures: I.E. Zapedowska:** None. **L.M. Molina-Martínez:** None. **J. Juárez:** None.

**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.15/NN3

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** Psychology Dept Endowment Fund

**Title:** Behavioral effects of long-term SSRI exposure in mice

**Authors: A. ROMPORTL**, E. SARGSYAN, *S. DICKINSON;
Psychology, St Olaf Col., Northfield, MN

**Abstract:** Selective Serotonin Reuptake Inhibitors (SSRIs), including fluoxetine, are the most commonly prescribed and studied antidepressants, though most preclinical work has not involved treatment periods of more than a month or two. We assessed the behavioral effects of six month exposure to fluoxetine through drinking water starting during adolescence (PND 36) in C57BL/6N mice (16 female, 16 male), relative to age-matched groups drinking plain water. To our knowledge, such long-term exposure has not previously been seen in the literature. Binge drinking was evaluated at several time points across development using a variation of the Drinking in the Dark procedure. In adulthood, behaviors related to anxiety and depression were also assessed. By three weeks of exposure, fluoxetine-treated mice weighed more than controls, and this difference persisted throughout the experiment. This weight gain was more significant in

the females. Using the Drinking in the Dark procedure, we found that female mice drank significantly more ethanol compared to male mice across all ages, but there was no consistent effect of fluoxetine treatment. In the Forced Swim Test, we found that fluoxetine significantly increased immobility in females, but not males. This could indicate behavioral despair in the drug group, although immobility could also indicate decreased anxiety and concomitant escape behaviors. Finally, in our last behavioral assay, the Light Dark Transition Test, we saw a trend towards increased anxiety in males on fluoxetine. Our findings suggest that long-term chronic SSRI exposure, beginning in adolescence, may result in effects contrary to those seen with short term drug treatment. Future research on supra-chronic SSRI use, especially relating to anxiety, is needed to determine the mechanisms and generality of our findings.

**Disclosures: A. Romportl:** None. **E. Sargsyan:** None. **S. Dickinson:** None.

**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.16/NN4

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** NIAAA grant R03AA025213 (JH)
University of Maryland BSOS Dean Research Initiative Doctoral Dissertation Fellowship (TH)
University of Maryland Maryland Summer Scholars Program (MMW)

**Title:** Personal space during social isolation affects alcohol sensitivity in crayfish

**Authors: *T. HO**[1], M. M. WILLIAMS[2], J. HERBERHOLZ[1,2];
[1]Program in Neurosci. and Cognitive Sci., [2]Dept. of Psychology, Univ. of Maryland, Col. Park, College Park, MD

**Abstract:** Social isolation causes detrimental impacts on human health, including an increase in alcohol use. Despite this, our understanding of the neural basis behind the interactions of social isolation and alcohol intoxication is limited. Prior work in our lab demonstrated that crayfish are a suitable model to investigate the neurobehavioral and neurocellular mechanisms underlying the interplay between prior social experience and ethanol (EtOH) sensitivity. Specifically, we found that acute EtOH exposure in juvenile and adult crayfish elicited a sequence of discrete behavioral changes, which included spontaneous tail-flips followed by motor incoordination. Moreover, one week of social isolation significantly reduced behavioral EtOH sensitivity compared to group-housed animals. These social effects were also observed on the level of single neurons - namely, the giant interneurons that control tail-flip behavior. In our current work, we focused on how different conditions of isolation (i.e., variation in personal space) impacts EtOH sensitivity. To study this, we isolated crayfish in tanks of two different sizes for 7 days, prior to EtOH exposure. Interestingly, we discovered that crayfish isolated in larger tanks (LT) produced EtOH-induced

spontaneous tail-flipping much later compared to animals isolated in smaller tanks (ST), indicating that isolation space affected EtOH sensitivity. Next, we used systemic injections of an antagonist against muscarinic acetylcholine receptors (mACh-Rs) before EtOH exposure to explore if the relationship between isolation space and EtOH sensitivity is regulated by changes in cholinergic neurotransmission. Because the sensory pathway that excites the lateral giant (LG) escape neurons, which mediate tail-flipping, contains nicotinic cholinergic synapses between the sensory afferents and interneurons as well as autoinhibitory mACh-Rs on the afferents, we hypothesized that different isolation conditions might lead to differences in ACh release and/or mACh-R expression. Our data show that blocking mACh-Rs significantly increases EtOH sensitivity in crayfish of both groups (LT & ST), and initial findings suggest a larger effect in animals that were isolated in LT. Taken together, our results indicate that larger personal space during isolation correlates with lower EtOH sensitivity in crayfish, and this reduction in EtOH sensitivity might be modulated, at least partly, by a change at the ACh synapses that are presynaptic to the tail-flip neurons. To confirm this hypothesis, we will employ intracellular electrophysiology and neuropharmacology on the LG circuit of animals with different isolation experiences.

**Disclosures:** **T. Ho:** None. **M.M. Williams:** None. **J. Herberholz:** None.

**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.17/NN5

**Topic:** G.09. Drugs of Abuse and Addiction

**Title:** Effect of binge-like alcohol exposure on extinction learning and subsequent voluntary drinking in adolescent vs adult CB57BL/6J female mice

**Authors: *X. LAY**;
Anat. & Neurobio., Univ. of Puerto Rico-RCM, Carolina, Puerto Rico

**Abstract:** Post-traumatic stress disorder (PTSD) and alcohol use disorder (AUD) are common comorbid conditions that affect a large part of the population, especially females. Studies have shown that it has sex and age-dependent effects on behavior as well. Fundamentally, we aimed to elucidate the effect on extinction learning after binge-like alcohol exposure on adolescent and adult female C57BL/6J mice to further understand the effect of binge-like alcohol consumption on learning memory and subsequent alcohol intake. We implemented a context fear conditioning (CFC) and context fear extinction (CFE) paradigm combined with a Single Episodic Ethanol (SEE) paradigm on both female adolescent (PD 28-53) and adult (PD 55-79) followed by an every- other-day (EOD) drinking procedure. Adolescents and adults were cycled prior to and during experimental procedures days. Adolescent and adult female mice that received ethanol injections during the SEE exposure did not exhibit any difference when compared to the mice that received saline injections during all three context fear extinction trials. When analyzing data

segregated by estrous stage, ethanol injected adolescents in estrus during extinction trials exhibit more freezing during the third trial than saline injected mice. Ethanol injected adults in diestrus during the extinction trials exhibit less freezing during the second trial. During EOD, both adults and adolescent females showed no difference in consumption between the ethanol and saline groups. We conclude that binge-like alcohol exposure after context fear conditioning, in both adult and adolescent female C57BL/6J wild type mice, does not affect fear extinction learning and subsequent voluntary ethanol consumption nor preference. Furthermore, estrous staging data suggests there is an influence of cycle stage on context fear extinction learning after binge-like alcohol exposure.

**Disclosures: X. Lay:** None.

**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.18/NN6

**Topic:** G.09. Drugs of Abuse and Addiction

**Title:** Wheel running as a possible model of behavioral sensitization following acute and subchronic dosing of ethanol in rats

**Authors:** J. JIAN[1], W. B. STEWART[1], U. A. MODI[1], ***J. RODEFER**[2,1];
[1]Neurosci., Mercer Univ., Macon, GA; [2]Comparative Med., Wake Forest Univ. Sch. of Med., Winston Salem, NC

**Abstract:** Alcohol use disorder (AUD) is a serious health problem that impacts about 30 million individuals, both youths and adults, in the United States each year. Demographic data from Substance Abuse and Mental Health Services Administration (SAMHSA) suggest that AUD has cross cultural impacts and certain groups (e.g., multi-race individuals, indigenous populations) may be particularly vulnerable to developing problematic behaviors with alcohol. Behavioral observations suggest that escalating use of alcohol may be associated with behavioral sensitization, or the increase in reinforcement value of alcohol following repeated administration. However, efficient examination of factors related to related to AUD are complicated by the finding that many laboratory-based translational studies utilize rodent models, many of which have inherent limitations (cf, Nieto et al. 2021). Thus, finding reliable methods to evaluate factors contributing to AUD is paramount to better understanding the disorder. One proposed metric of behavioral sensitization is voluntary wheel running behavior following drug administration (Niculescu et al. 2022). We used a between subject design to evaluate the effect of acute and subchronic administration of ethanol across a range of doses (0.1-0.5 g/kg) or vehicle in both male and female Long Evans rats (n=24). Subjects experienced a 10-d procedure with ethanol administration occurring on days 1-5. On day 10, all animals received a challenge dose of the intermediate dose of ethanol. Voluntary wheel running trials were measured on days 1, 5, and 10. No behavioral manipulations or assessments occurred on days 6-9. A repeated

measures two-way factorial analysis of variance (ANOVA) was performed to analyze the effects of ethanol dose treatment and days on wheel running behavior across the duration of the experiments. Data suggested a trend such that administration of the lowest doses resulted in increased mean wheel running behavior across the 10 days whereas the highest dose examined tended to decrease wheel running behavior across days. Taken together, these data may suggest that voluntary wheel running behavior might be useful and serve as a metric of behavioral sensitization to the effects of ethanol administration in some strains of rodents.

**Disclosures: J. Jian:** None. **W.B. Stewart:** None. **U.A. Modi:** None. **J. Rodefer:** None.

**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.19/NN7

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** R01AA026306
R01AA027213
F31AA030921

**Title:** Central Amygdala Activity During an Ethanol Self-administration Task Dynamically Tracks Motivation State

**Authors: *M. CASTRO**[1], C. DRIEU[2], D. OTTENHEIMER[4], T. DONG[2], S. ZHANG[2], P. JANAK[1,2,3];
[1]Dept. of Neurosci., [2]Dept. of Psychological and Brain Sci., [3]Kavli NDI, Johns Hopkins Univ., Baltimore, MD; [4]NAPE Ctr., Univ. of Washington, Seattle, WA

**Abstract:** The central nucleus of the amygdala (CeA) is likely involved in regulating motivational drive to consume ethanol (EtOH) and other rewards. Our lab has recently described a subpopulation of CeA neurons that was modulated during EtOH consumption in a free-drinking task. We next sought to understand how CeA neurons fire as an animal must work to self-administer a reward, a process that is sensitive to changes in motivation. Here we recorded extracellular spike activity of CeA neurons while rats self-administered EtOH using a discrete trials 3 (DT3) task, in which Long Evans rats (n=6 4F/2M, age>P60) had to make 3 lever presses within 60 sec of lever insertion after which the lever was retracted and 0.2 ml 10% EtOH was delivered in the adjacent port (30 rewards or 50 trials per session; 30s ITI). We collected 877 neurons over 15 recording sessions. Many neurons displayed significant responses to events related to the cue, lever press, and alcohol consumption. To test whether neural correlates changed as motivation to drink waned, we compared neural responses to the first 5 and last 5 cue presentations (e.g., lever insertion) and found significantly larger responses to the first 5 lever insertions compared to the last 5 lever insertions, as determined by area under the curve (paired one-tailed t-test; inhibitions, $p<0.005$ / excitations, $p<0. 0001$). Next, we classified individual

trials as high or low motivation based on the latency to first lever press and plotted the respective deviations in event-related firing from the baseline. The most pronounced difference between these curves occurred at the time of the lever insertion cue. We then sought to determine if the strength of the cue-evoked activity was correlated with behavioral metrics for task engagement, namely latency to first lever press, time taken to complete the 3 lever press ratio, and time to port entry following ratio completion. We found that cue-evoked activity was significantly negatively correlated with log-transformed latency to first press in 12% of neurons (Pearson's correlation; $p \leq 0.05$), suggesting that some CeA neurons are more activated by lever insertion when motivation to engage with the task is high. We also analyzed CeA activity during EtOH lick bouts; using a Rayleigh test, we found that ~44% of neurons were lick-modulated, and that all rats displayed lick-modulated neurons. Lick-modulated neurons tend to fire early in the lick cycle, just after the lick is made. Taken together, our work supports the notion that the CeA reflects motivational state over the course of drug self-administration.

**Disclosures: M. Castro:** None. **C. Drieu:** None. **D. Ottenheimer:** None. **T. Dong:** None. **S. Zhang:** None. **P. Janak:** None.

**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.20/NN8

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** NIGMS Graduate Research Training Initiative for Student Enhancement (G-RISE) Grant (T32-GM144876), G-RISE at UMBC

**Title:** Anchor protein modulates ethanol-related behaviors in a drosophila knockdown model

**Authors: *E. JOHNSON**, K. CHESNUT, F. VONHOFF, L. SUTTON;
Biol., Univ. of Maryland, Baltimore County, Baltimore, MD

**Abstract:** Recent molecular evidence suggests that mammalian GPR155, a marker of the dorsolateral striatum, could play a role in mechanisms underlying ethanol-related behavior. Here, we focus on anchor, the Drosophila homolog of GPR155. We performed a behavioral screen with a pan-neuronal knockdown of anchor in Drosophila melanogaster in order to rapidly and efficiently clarify its role in ethanol related behavior. We found that both male and female flies with pan-neuronal anchor knockdown sedated significantly slower in the presence of ethanol vapor compared to genetic control lines. In a measure of olfactory ethanol attraction, consistent with published results, virgin control males were attracted to ethanol, while mated control males were repelled by it. However, these ethanol preferences were reversed in pan-neuronal anchor knockdown males. Similarly, while both mated and non-mated control females are repelled by the scent of ethanol, anchor knockdown females were attracted to it. Overall, results indicate that anchor knockdown increases Drosophila resistance to ethanol-induced sedation and that it

reverses olfactory ethanol preference. Findings not only identify a behavioral role of anchor but also suggest that it could be a novel target of ethanol research. We plan to use findings to inform future studies of rodent ethanol-induced sedation and ethanol preference.

**Disclosures:** **E. Johnson:** None. **K. Chesnut:** None. **F. Vonhoff:** None. **L. Sutton:** None.

**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.21/NN9

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** NIH Grant 5P20GM103642
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NIH Grant 2R25NS080687
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**Title:** Epigenetic modeling involved in ethanol response affects sleep behavior of Drosophila melanogaster

**Authors: *S. MORALES CANCIO**, C. D. DEL VALLE-COLÓN, N. L. FUENZALIDA-URIBE, A. GHEZZI;
Univ. de Puerto Rico, Rio Piedras, San Juan, PR

**Abstract:** According to the National Institutes of Health (NIH), a significant percentage of adults (7-19%) experience insufficient sleep, and approximately 60 million Americans suffer from chronic sleep disorders. Additionally, alcohol abuse has been shown to cause sleep disturbances by affecting gene expression and sleep homeostasis. Using Drosophila melanogaster flies to assess the neuroadaptations induced after ethanol exposure, has made it possible to identify several alcohol-responsive genes involved in these processes. Particularly, transcriptomics approaches have shown epigenetic mechanisms as essential to ethanol sensitivity and tolerance acquisition. Here we focus on investigating the role of epigenetic modulators genes that encode the histone acetyltransferases in modulating Drosophila's sleep behavior. The ventrolateral neurons (LNv) are considered the "main core" of the fly's circadian rhythms and control sleep homeostasis; thus, we wonder whether epigenetic mechanisms involved in ethanol neuroadaptation affect sleep behavior in Drosophila. We disrupted two epigenetic modulators genes (Tip60 and nej), which encode the histone acetyltransferase TIP60 and CBP, respectively. For this, we used the UAS-GAL4 system to express RNAi to knock down these genes into the LNv neurons and monitored the effects of this manipulation on sleep behavior in adult female

flies. Our data show that flies expressing RNAiTip60 in the LNv neurons have decreased fraction of time sleeping, suggesting Tip60 knockdown into LNv plays a role in modulating sleep behavior in flies. Moreover, expressing RNAinej increases the fraction of time sleeping in flies. We propose epigenetic modulators play a role, not only in regulating ethanol responses in flies but also in modulating sleep homeostasis with ethanol-responsive genes as modulators of LNv gene expression necessary to develop normal sleep behavior.

**Disclosures: S. Morales Cancio:** None. **C.D. Del Valle-Colón:** None. **N.L. Fuenzalida-Uribe:** None. **A. Ghezzi:** None.

**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.22/NN10

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** NIH Grant R01 AA015614
NIH Grant P50 AA022534

**Title:** Binge ethanol exposure during the brain growth spurt has long-lasting effects on memory engrams in mice

**Authors: *K. LOPEZ**[1], S. MAYFIELD[2], A. FLORES[2], B. DUNN[2], G. HOLTZMAN[2], R. ALMEIDA-MANCERO[2], D. GHATALIA[2], J. PATEL[2], E. GORANSON[2], E. ESTRADA[2], C. PADILLA[2], G. CHAVEZ[2], J. KELLY-ROMAN[2], C. VALENZUELA[2];
[1]Univ. of New Mexico Dept. of Neurosciences, Albuquerque, NM; [2]Dept. of Neurosciences, Sch. of Med., Univ. of New Mexico Hlth. Sci. Ctr., Albuquerque, NM

**Abstract:** Prenatal exposure to alcohol is a widespread cause of intellectual disability, leading to a range of effects known as Fetal Alcohol Spectrum Disorders. The detrimental impact of ethanol on the fetal brain can occur at any stage of pregnancy, including the crucial final trimester when significant brain growth occurs. Exposure to ethanol during this late pregnancy period can result in long-lasting learning and memory impairments extending into adulthood. Research indicates that these deficits may be a consequence of apoptotic neurodegeneration within the posterior limbic memory system. This intricate system encompasses specialized neuronal populations within interconnected regions including the retrosplenial cortex, hippocampal formation, and anterior thalamic nuclei. This study tested the hypothesis that third-trimester-equivalent ethanol exposure would result in long-lasting alterations in memory engrams in these brain regions. To test this hypothesis, Fos2A-iCreER/1(TRAP2) mice crossed with ROSA26-CAG-stop-floxtdTomato were injected at postnatal day 7 (P7) with 2 doses (2 hr apart) of 2.5 g/kg of ethanol or saline subcutaneously and left undisturbed until adulthood. Contextual fear conditioning was performed and 4-hydroxytamoxifen was injected ~2 hr after memory retrieval (on day 2 of the behavioral paradigm) to cause translocation of Cre

recombinase to the nucleus and drive expression of tdTomato in activated neurons. Brains were sectioned in the coronal plane with a cryostat and mounted in media containing the nuclear stain, DAPI. Images were obtained with an Axioscope slide scanner. The numbers of tdTomato positive neurons in the retrosplenial cortex, hippocampal formation, and anterior thalamus were quantified using QuPath software using a brightness threshold and density counts. Ethanol exposure significantly ($p=0.0026$) reduced the percent freezing time on day 2 by 23%. The CA1 and CA3 hippocampal regions exhibited a greater abundance of td-Tomato-positive cells, indicating heightened activation of a distinct memory engram in ethanol-exposed animals. Conversely, no notable differences were observed in the dentate gyrus, retrosplenial cortex, or anterior thalamus. These findings imply that the activation of distinct hippocampal neuronal populations is associated with ethanol-induced memory retrieval disruptions. Ongoing studies aim to explore whether this increased hippocampal activation contributes to deficits in memory retrieval or functions as a compensatory mechanism to address impairments in other nodes of the limbic memory network.

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**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.23/NN12

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** Butler University HAC award
Indiana Academy of Science

**Title:** The effects of increasing amounts of caffeine on alcohol intake in C57BL/6J mice

**Authors:** A. KAUR, ***J. N. BERRY**;
Psychology, Butler Univ., Indianapolis, IN

**Abstract:** Two of the most popular and legal drugs around the world are caffeine and alcohol. Both drugs are easily accessible in America, and this has led to the two drugs being used in frequent combination with one another. Large quantities of caffeine can have adverse effects alone and drinking alcohol while consuming caffeine can pose additional health concerns. It has been theorized that consuming alcohol while also consuming caffeinated beverages may modify or "disguise" an individual’s perceived consciousness of intoxication. The probability of partaking in various harmful behaviors while inebriated could rise as a consequence of the suggested reduction in perceived intoxication, which could have catastrophic repercussions. Although each substance has been extensively studied individually, the implications of co-

consumption are still not entirely known. Previous research has resulted in mixed effects, thus the combination warrants further investigation. A recent study from our lab suggested dose-dependent effects where intermittent access (IA) to consistent levels of low (0.015%) but not moderate (0.03%) caffeine increased alcohol consumption in male C57BL/6J mice. In the current study, the effects of increasing caffeine concentrations (0.01-0.03% w/v) on a consistent, low alcohol concentration (10% v/v) were studied. C57BL/6J mice (*n*=24; 12 males and 12 females) were exposed to the experimental drug bottles intermittently every 24 hours. Fluid consumption was recorded daily for four weeks and mice were then individually tested in an open field test (OFT) to assess anxiety-like behaviors during withdrawal approximately 6 hours after removal of the drug bottles. Similar to previous results, male mice consumed more alcohol overall when it was mixed with caffeine compared to male mice exposed to alcohol alone; this pattern was not found in female mice, however, as females exposed to 10% alcohol alone consumed relatively high amounts of alcohol throughout the entirety of the experiment. The results from the OFT revealed no significant difference between experimental groups and no differences between male and female mice. These results are consistent with a dose- and sex-dependent nature of caffeine-mixed alcohol consumption in mice. More research is necessary to determine the psychological effects of withdrawal from these drugs.

**Disclosures: A. Kaur:** None. **J.N. Berry:** None.

**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.24/NN13

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** Universidad Iberoamericana

**Title:** Prolonged periods of maternal separation do not induce a high voluntary ethanol intake in male rats

**Authors: *S. MU?OZ SANCHEZ**[1,3,4], L. RODRIGUEZ SERRANO[3], O. GALICIA[1], C. HERNANDEZ-GUERRERO[2], C. CRUZ-FUENTES[4], M. BUENROSTRO JAUREGUI[1]; [1]Psicología. Lab. de Neurociencias., [2]Univ. Iberoamericana. Ciudad de México, Mexico, Mexico; [3]Psicología., Univ. Anáhuac., Estado de Mexico, Mexico; [4]Genetica, Inst. Nacional de Psiquiatria Ramon de la Fuente Muñiz, Ciudad de Mexico, Mexico

**Abstract:** Adverse events promote states of stress. Stress models in the early stages of development in animal models are widely used in various fields of neuroscience. Maternal separation (MS) in rodents is an animal model of early stress, causing neurochemical and behavioral alterations in the offspring that persist into adulthood. We used an MS model after birth in male Wistar strain rats. The rats used were housed within a regular light cycle (0800 to 2000). We compare two temporary-term MS model procedures: the short-term was achieved

during postnatal days 2 to 15 (180 minutes, 1100 to 1400). The long-term was executed during postnatal days 2 to 21 (180 minutes, 1100 to 1400). The animals had free access to food and water in their house case. At postnatal day 50, we start the alcohol test procedure. During the habituation phase, four days before the experiment, the water bottle (500 ml) was removed from each cage and replaced with two smaller water bottles (100 ml). Then, animals were exposed to an alcohol solution in gradually increasing concentrations. We use four different concentrations, corresponding to 2%, 4%, 6%, and 8% v/v. Each of these concentrations was offered for four consecutive days, to which the animals had free access. The location placement of the water bottles and alcohol in the cage was changed daily in position to avoid place preference, and their volumes were weighed every 24 hours. Alcohol concentrations were prepared fresh every day by mixing the corresponding ethanol solution with tap water. The amount of alcohol consumed was calculated individually for each rat. The amount of consumption is expressed as g/kg. The alcohol preference ratio was also determined as alcohol intake versus water intake.Our results showed that animals exposed to three weeks of MS showed a lower preference for alcohol compared to animals with two weeks of MS. Also, animals treated with MS showed higher levels of anxiety compared to controls. This is in concordance with other literature data that also report changes related to the time of separation. In terms of neurobiological consequences of MS, conclusive data are sparse and one of the future challenges will be identifying and characterizing underlying neurobiological mechanisms, especially in the individual animal.

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**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.25/NN14

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** PAPIIT IN300122 (UNAM, Mexico)

**Title:** Intra-accumbal administration of GABAB receptors agonist baclofen reduces the effects of nicotinic acetylcholine receptor agonist cytisine on oral self-administration of ethanol in rats

**Authors: *F. MIRANDA-HERRERA**[1], J. C. JIMENEZ[2], A. I. BARRIENTOS-NORIEGA[3]; [1]Univ. Nacional Autonoma De Mexico, Tlanepantla, Edo Mex, Mexico; [2]Psychology, FES Iztacala UNAM, Mexico City, Mexico; [3]Facultad de Estudios Superiores Iztacala, Mexico, Mexico

**Abstract:** INTRODUCTION. The mesocorticolimbic dopamine (DA) system plays a key role in mediating addictive effects of ethanol (EtOH). This system is comprised of DA neurons in the ventral tegmental area (VTA) that project their axons to nucleus accumbens (nAcc) and other limbic structures. Although mesocorticolimbic DA system is the main neurochemical substrate

for regulating the addictive effects of EtOH, other neurotransmitter systems modulate DAergic function in nAcc such as acetylcholine (Ach). Ach is released from cholinergic interneurons in nAcc and their actions are induced through binding to nicotinic and muscarinic Ach receptors. Previously, we reported that intra-accumbal administration of nicotinic Ach receptor agonist cytisine increased oral self-administration of EtOH. GABAB receptors in the nAcc are expressed in the DAergic nerve endings and play an inhibitory role in the regulation of DA release into the nAcc and could modulate the effects of cytisine on oral self-administration of EtOH. The present study was designed to assess the effects of intra-accumbal administration of the GABAB receptor agonist baclofen (BCF) on the effects of cytisine on oral self-administration of EtOH. METHOD. Male Wistar rats were used. Rats were water deprived for 23.30 h, and then trained a lever-press for water reinforcement on a FR1 schedule by 3 days. Then, rats were trained to lever-press for EtOH (0.01 ml of EtOH in water at 12%) on a FR1 schedule by 3 days. After this training, the reinforcement contingency was changed to FR3 for EtOH access until response rate remained stable at 80%. After this behavioral training, rats received intra-accumbal injection of BCF (0.01, 0.02, 0.04 μg) or cytisine (0.8, 1.6, 3.2 μg) or the combination of BCF (0.04 μg) + cytisine (0.8, 1.6, 3.2 μg). Each dose per session test, cannulae were implanted at nAcc shell (AP +2.0 mm of Bregma, ML ± 0.8 mm, DV -4.5 mm). RESULTS. The data showed that intra-accumbal injections of cytisine increased oral self-administration of EtOH, while BCF reduced the oral self-administration of EtOH. The effects of cytisine was reduced by BCF administration These findings suggest that GABAB receptor agonist modulate the increase of oral self-administration of EtOH produced by cytisine.

**Disclosures: F. Miranda-Herrera:** None. **J.C. Jimenez:** None. **A.I. Barrientos-Noriega:** None.

**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.26/NN15

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** R01 DA042499
R01 DA041781
R01 DA045463

**Title:** Inflammatory pain promotes alcohol self-administration in female rats: the dose and sex matter

**Authors: *Y. CAMPOS-JURADO**, Y. M. SAAD, B. ZAHOOR, H. LATIF-JANGDA, J. A. MORON;
Anesthesiol., Washington Univ. in St. Louis, Saint Louis, MO

**Abstract:** During the last years, multiple clinical and epidemiological studies have revealed that the presence of chronic pain is closely related to Alcohol Use Disorder (AUD). However, there is only a limited number of preclinical studies approaching this problematic and therefore the specific effect of pain on AUD remains not fully discern. In this study we aimed to deeply explore wether the development of an inflammatory pain condition induced by the intraplantar injection of the Complete Freud Adjuvant (CFA) could impact alcohol self-administration (ASA) in animals with a previous history of alcohol exposure. For that, after being exposed to alcohol in their homecages using the drinking in the dark protocol during 2 weeks, male and female rats were trained to self-administer 20% alcohol in a FR3 schedule of reinforcement. Once ASA was stable across days, rats were injected with CFA or saline into their hind-paws. Then, they were subjected to a dose-response test, consited of 3 consecutive sessions for each of the alcohol doses (20%, 30% and 50%), presented in a randomly assigned, ascending or descending manner. Our results show that only CFA treated females increased their total alcohol intake at the higher dose of 50% alcohol. However, in males, there was not an effect of inflammtory pain on alcohol intake levels. These findings may contribute to the better understanding of the intersection between pain, AUD and the potential sex differences, and to the development of more individualized treatments for chronic pain patients with a history of alcohol abuse.

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**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR045.27/NN16

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** F31AA029297
T32AA07462
R01AA027214

**Title:** The role of the anterior insular cortex inputs to the dorsolateral striatum in binge alcohol drinking

**Authors: *D. L. HAGGERTY**[1], B. MUÑOZ[1], T. PENNINGTON[2], G. GONZALO VIANA DI PRISCO[2], G. G. GRECCO[3], B. K. ATWOOD[3];
[1]Pharmacol. and Toxicology, [3]Indiana Univ. Sch. of Med., [2]Indiana Univ. Sch. of Med., Indianapolis, IN

**Abstract:** How does binge drinking alcohol change synaptic function, and do these changes maintain binge consumption? The anterior insular cortex (AIC) and dorsolateral striatum (DLS) are brain regions implicated in alcohol use disorder. In male, but not female mice, we found that binge drinking alcohol produced glutamatergic synaptic adaptations selective to AIC inputs

within the DLS. Photoexciting AIC --> DLS circuitry in male mice during binge drinking decreased alcohol, but not water consumption and altered alcohol drinking mechanics. Further, drinking mechanics alone from drinking session data predicted alcohol-related circuit changes. AIC --> DLS manipulation did not alter operant, valence, or anxiety-related behaviors. These findings suggest that alcohol-mediated changes at AIC inputs govern behavioral sequences that maintain binge drinking and may serve as a circuit-based biomarker for the development of alcohol use disorder.

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**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.28/NN17

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** NIH grant R01 AA026306
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**Title:** Chronic ethanol vapor exposure in adult rats reduces behavioral flexibility in protracted withdrawal

**Authors: *Y. CHENG**[1], R. MAGNARD[2], C. DRIEU[3], E. GARR[3], L. CASTELL[3], A. CHARLES[4], A. LANGDON[5], D. LEE[6], P. H. JANAK[3];
[2]Janak Lab., [3]Johns Hopkins Univ., [1]Johns Hopkins Univ., Baltimore, MD; [4]Johns Hopkins Univ. - Homewood Campus, Lutherville-Timonium, MD; [5]Natl. Inst. of Mental Hlth., Natl. Inst. of Mental Hlth., Bethesda, MD; [6]Johns Hopkins Univ., Johns Hopkins Univ. - Main Campus, Baltimore, MD

**Abstract:** Alcohol use disorder has been linked to sustained cognitive dysfunction. Increasing evidence suggests prolonged alcohol consumption impairs adaptive behavioral control over alcohol-seeking behavior. Prior studies have shown that chronic alcohol exposure induces aberrant plasticity in the dorsomedial striatum (DMS), a critical structure involved in flexible behavior. However, the degree to which chronic alcohol exposure has long-term impacts on flexible decision processes and underlying neuronal dynamics in the DMS remains unclear. We hypothesized that chronic alcohol exposure reduces animals' ability to adapt their behavior in non-stationary environments and evoke aberrant representations of choice and outcome in the DMS. To test this hypothesis, 17 male Long Evans rats were trained to perform a dynamic probabilistic reversal learning task with binary choices that contained blocks with varying reward (10% sucrose water) probability schedules. Rats were either exposed to ethanol vapor in a chronic intermittent (CIE, n=8) schedule over 4 weeks to mimic human alcohol dependence level (>150mg/dl of blodd) or air (n=9, control) in the same condition. After 10 weeks withdrawal, we

collected behavioral data and recorded DMS neural spikes. We found that CIE rats showed a slower reversal speed ($\lambda = 0.21$) than the air controls ($\lambda = 0.4$) when the reward probabilities transitioned from a relatively low uncertainty setting to a relatively high one ($p = 0.012$). CIE rats also exhibited other behavioral differences to controls across multiple domains. Support vector machine traied with a multi-dimensional behavior dataset pooled from above domains achieved ~67% accuracy on predicting 2 group memberships, and ~43% on predicting 17 individual identities. To reveal how CIE alters the computations underlying choice behavior, we fit reinforcement learning models on trial-basis behavioral data and found that CIE enhanced the learning rate on the rewarded outcome. To understand how alcohol alters the encoding of choices and outcomes in the DMS, we fit a multivariate regression model on striatal spikes as a function of the history of choices and outcomes. We found that the representation of the current trial outcome was stronger, whereas the representation of the choice-outcome interaction was weaker, in CIE rats than in air controls. These results indicate that CIE alters goal-directed decision processes in the DMS, thus leading to a loss of adaptive control of action selection. Together these findings unveil the behavioral and neural processes that underpin the detrimental effects of chronic alcohol use on cognitive functions.

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**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.29/NN18

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** BGSU Psychology Department Fund

**Title:** Sugar and ethanol reward relativity in alcohol preferring (P) rats: A focus on an incentive contrast paradigm and mesocorticolimbic anatomy

**Authors: *K. THOMPSON**[1], E. SHULTZ[1], H. C. CROMWELL[2];
[2]Bowling Green State Univ., [1]Bowling Green State Univ., Bowling Green, OH

**Abstract:** During withdrawal, many individuals with Alcohol Use Disorders (AUD) report having strong cravings for sweet products. Research has revealed that individuals with high cravings for sweeter products take ten times longer to attain abstinence and have higher relapse rates than those who do not have high sweet cravings. Furthermore, research has indicated that sugar intake alone can induce changes that are similarly produced by drugs of abuse and AUD. Animal studies using alcohol preferring (P) rat models have observed functional changes which occur in the reward pathways (mesocorticolimbic and nigrostriatal pathways) of the brain when sugar is consumed; these studies have further indicated that sugar can have a similar effect on the reward pathways as alcohol intake. The current project aims to use an incentive contrast

paradigm to explore response sensitivity to shifts in time access intervals for both sugar and ethanol concentrations. Preliminary results suggest that P rats can discriminate between time changes for sucrose; demonstrated behaviorally by changing their responses in nose poke rates, licking rates, and consumption depending on the time access. However, this did not translate to ethanol, instead P rats had a generalization effect between the time access trials. Preliminary results also imply that P rats show trends for positive contrast but not negative contrast for sucrose and the opposite for ethanol. The current project also aims to compare neuroanatomy of the striatum (putamen and caudate) and the nucleus accumbens (NAc) between P rats and Wistar strain by comparing dopaminergic fibers (tyrosine hydroxylase stain), and total cell counts (nissl). This research could provide insight to the connection to high sugar diets, sugar addictions, and AUD.

**Disclosures: K. Thompson:** None. **E. Shultz:** None. **H.C. Cromwell:** None.

**Poster**

**PSTR045. Alcohol Cognitive and Behavioral Effects**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR045.30/NN19

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** BGSU Psychology Department Funds

**Title:** Comparing natural and drug reward sensitivity in rat model: A focus on incentive contrast in non-food restricted animals

**Authors: *E. L. SHULTZ**[1], K. THOMPSON[2], H. C. CROMWELL[3];
[1]Psychology, [2]465 S. Summit, APT 42, [3]Bowling Green State Univ., Bowling Green State Univ., Bowling Green, OH

**Abstract:** According to the CDC, 29.5 million Americans had a diagnosis of alcohol use disorder (AUD) in 2021. Shared reward pathways in the brain unveil the potential for the development of dependence on a variety of substances, including commonly recognized drugs of abuse and, more insidiously, sugar. Sugar overconsumption has been associated with compulsivity and impulsivity repetitive behaviors which are predictors of later substance abuse. Furthermore, previous research has shown that rats can develop symptoms mirroring addiction such as binging, craving, tolerance, and withdrawal in response to sugar alone. Motivation research has indicated that impaired reward relativity is a key component of vulnerability to addiction. The ability of an animal to discriminate between differing levels of rewards for the amount of work exerted to receive that reward may predict later addictive behavior to a variety of substances. This study examined the appetitive and consummatory behavior of female Wistar rats in self-administration tasks of sucrose and ethanol solutions. The rats had ad-libitum access to food and water and relative reward effects were evaluated by using trials that differed in time of access to the reward (20s vs 10s vs 5s). Data of volume consumed, nosepoke latencies, lick

rate, and lick latencies were reviewed. These were then analyzed to examine incentive contrast effects and to determine if previous behavior in response to sucrose had predictive potential of later response to alcohol. Preliminary results show increased consumption of sucrose in comparison to ethanol and indicate that Wistar rats discriminate between trial types for both sucrose and ethanol. The rats also showed predictable incentive contrast responses to trials involving sucrose. Notably, they displayed faster nosepoke latencies during positive contrast ethanol trials while maintaining similar lick latencies and consumption volume, suggesting more sensitivity during the appetitive than consummatory phase. Overall, the Wistars showed more sensitivity for sucrose compared to ethanol, as they drank less ethanol and showed lower levels of incentive contrast. The incentive contrast paradigm used in the current study allows a closer examination of the motivational processes shared by alcohol and sugar that could result in addiction. Using natural reward sensitivity to predict future addiction could aid significantly in preventing and treating substance use disorders.

**Disclosures: E.L. Shultz:** None. **K. Thompson:** None. **H.C. Cromwell:** None.

**Poster**

**PSTR046. Cannabinoids: Behavioral and Neural Mechanisms and Addiction**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR046.01/NN20

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** California Department of Cannabis Control (Award#65374) to D.G.G

**Title:** Neurobehavioral responses to legal cannabis advertisements in youth and adults: Preliminaryfindings with policy implications

**Authors: J. CHEN**[1], R. ZHANG[1], *N. CHABIN[2], A. PADON[3], L. SILVER[3], D. G. GHAHREMANI[1];
[1]Dept. of Psychiatry and Biobehavioral Sci., [2]UCLA, Los Angeles, CA; [3]Publ. Hlth. Inst., Oakland, CA

**Abstract:** Exposure to marketing media for legal substances has a significant impact on subsequent substance use, with under-age youth especially susceptible to influence. Guidelines for regulating cannabis advertising are needed to protect underage youth in states where cannabis is legal. Identifying key features appealing to youth is an important step in specifying guidelines. The Content Appealing to Youth (CAY) index, developed for alcohol and tobacco advertisements (Padon et al. 2017, 2018), indicated key advertising features that are appealing to youth. We sought to modify the CAY index for cannabis ads using both behavioral and neural responses using fMRI, with an overall aim to inform policy guidelines for cannabis marketing. After modifying the CAY index using online surveys and focus groups, we presented cannabis ads (mostly social media posts) to youth and adults (range: 16-36 years old) during fMRI scanning. We identified non-cannabis control ads that matched cannabis ads for appearance.

After each ad presentation (20 s), participants rated how much they liked it. Eleven of 37 participants scanned used cannabis regularly. We first compared brain responses to cannabis and control ads to determine brain activation specific to cannabis content. Then, we compared responses to ads with low and high CAY content across age. We focused a priori on the ventral striatum and amygdala, given the role of these regions in reward processing, but exploratory whole-brain analyses were also conducted. We found that cannabis ads elicited greater activation in the amygdala and ventral striatum than control ads. This activation significantly correlated with participants' ad liking. Whole brain analyses showed greater activation in the precuneus for cannabis vs. control ads ($Z>3.1$, $P<0.05$). We observed an interaction of age and CAY on both ad liking and ventral striatum and amygdala responses to cannabis ads, such that youth showed greater ad liking and greater brain activation in these areas for high vs. low CAY ads, and adult responses to the two CAY levels were indistinguishable (both in liking ratings and brain activation). No effects of regular cannabis use were found in any analyses. These preliminary results indicate that the cannabis-sensitive CAY Index is validated by behavioral and brain experiments. They also indicate an important role for brain regions that underlie appetitive responses to drug cues in evaluating ad content. With respect to implications for policy, our results suggest that advertisements with features that are low on the CAY index will be effective for adults but potentially less so for youth. Guidelines may suggest to avoid high CAY content in ads.

**Disclosures: J. Chen:** None. **R. Zhang:** None. **N. Chabin:** None. **A. Padon:** None. **L. Silver:** None. **D.G. Ghahremani:** None.

**Poster**

**PSTR046. Cannabinoids: Behavioral and Neural Mechanisms and Addiction**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR046.02/OO1

**Topic:** G.09. Drugs of Abuse and Addiction

**Title:** Neuropeptide Y expression in the hypothalamus of cannabinoid-exposed adolescent rats

**Authors: B. MULHOLLAND**, H. A. KHAN, Z. M. HANNABASS, J. BLANCHETTE, M. L. ECKARD, P. A. JACKSON, *D. M. HAYES;
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**Abstract:** With changing state-level legislation and more drug availability than ever, data from the National Survey on Drug Use and Health revealed that approximately 2.1 million Americans aged 12-25 reported initiating use of cannabis in 2022 (NSDUH, 2020). Importantly, the initiation of use during adolescence and young adulthood is of particular importance due to a heightened vulnerability of the developing nervous system (Mooney-Leber & Gould, 2018). It is widely known that cannabis use can increase appetite. This change in hunger state appears to be mediated via endocannabinoid activity in the hypothalamus (Pagotto et al., 2006), but the nature of appetite and reward signaling in this region is complex with various overlapping

neurobiological pathways. Thus, assessing the effects of cannabinoid exposure on known hunger peptides, including Neuropeptide Y (NPY), may elicit an increased understanding of the hypothalamic circuitry. However, studies of cannabinoid exposure in adolescent rats in our laboratory have consistently revealed a reduction in body weight and food intake following administration, thus necessitating a nutritional control (Biscaia et al., 2003; unpublished data). Therefore, adolescent rats were randomly assigned to one of three conditions; drug+supplement, yoked+supplement, and weight-control. The supplement groups were allowed access to Vanilla Ensure throughout the injection period (CP-55,940 or vehicle; i.p.) from post-natal day (PND) 35-49. Following a battery of behavioral tests, animals were injected with sodium pentobarbital then transcardially perfused. Brains were extracted, post-fixed for 24 hours, then stored in PBS until processing. A vibrating microtome (Leica VT1000S) was used to coronally slice the whole brain into 40-micron sections. A 1:8 tissue series was utilized to examine the expression of NPY in the paraventricular nucleus of the hypothalamus following standard immunohistochemistry protocols with a 3% normal goat serum and rabbit anti-NPY primary antibody (BMA Biomedicals). NPY expression in the paraventricular nucleus was quantified via densitometric analysis of representative photomicrographs obtained using a BX-43 microscope (Olympus) and associated Q-Capture software (n = 9-10/group). Pixel density was determined using thresholding analysis within the Image J software package (NIH). One-way ANOVA failed to reveal any significant differences in NPY expression levels between groups, indicating a need for further investigation into the complicated mechanisms underlying the relationship between hunger and cannabinoid reward pathways within the hypothalamus.

**Disclosures: B. Mulholland:** None. **H.A. Khan:** None. **Z.M. Hannabass:** None. **J. Blanchette:** None. **M.L. Eckard:** None. **P.A. Jackson:** None. **D.M. Hayes:** None.

**Poster**

**PSTR046. Cannabinoids: Behavioral and Neural Mechanisms and Addiction**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR046.03/Web Only

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** PAPIIT MMD IA205218
PAPIIT AERC IN217121
PAPIIT OPG IN202822

**Title:** The social and mystical brain of marijuana users

**Authors: *J. GOMEZ VILLATORO**[1], Y. ALVARADO RAMÍREZ[2], E. CIPRÉS AGUILAR[2], A. HERRERA-SOLIS[3], A. E. RUIZ-CONTRERAS[2], O. E. PROSPÉRO GARCÍA[2], M. MÉNDEZ-DIAZ[2];
[1]Physiol., [2]UNAM, Coyoacan, Mexico; [3]Hosp. Gen. Dr. Manuel Gea González, Tlalpan, Mexico

**Abstract:** Worldwide drug consumption is estimated at 275 million people, of whom 31 million suffer from a substance use disorder (SUD), the most used drug is marijuana with 192 million users (UNODC, 2018). Diverse long-life experiences have been linked to the use of substance of abuse, including neglectful care, physical or sexual abuse, social interactions, and absence of religiosity or mysticism (Beck et al., 1973; Dermota et al., 2013). In this observational descriptive study pretend to describe whether parenting style, adaptive capacity, emotion identification, loneliness, and religiosity influence developing SUD. A total of 118 participants were evaluated (76 males, 42 females) between 18 to 54 years old. They were recruited through social networks. All participants signed an informed consent letter and responded register format, marijuana consumption questionnaire, parental bonding instrument (Parker, Tupling y Brown, 1979), theory of mind inventory (Hutchins et al., 2010), attitudes towards religiosity (Tinoco-Amador, 2006), substance use stigma mechanisms scale (Laramie, 2016), loneliness scale (Russell et al., 1980) and resilience scale (Gómez Valdez, 2010). The results reveled that 91% of the participants have consumed any substance of abuse, at least once in their lives. 61% of them having used marijuana. Age onset for marijuana consumption was 16 years. Positive social relationships are believed to promote physical and mental well-being and prevent substance abuse, while negative interactions may contribute to SUD.

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**Poster**

**PSTR046. Cannabinoids: Behavioral and Neural Mechanisms and Addiction**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR046.04/OO2

**Topic:** G.09. Drugs of Abuse and Addiction

**Title:** Cannabis Self-Administration: Exploring Sex and Region-Specific Impact on Perineuronal Nets in the Prefrontal Cortex of Rats

**Authors: *G. E. KIRKPATRICK**[1,3], G. I. PARK[1], V. WALLINGFORD[1], R. ABESHIMA[1], A. MALENA[1], P. YUNKER[1], R. J. MCLAUGHLIN[2], T. E. BROWN[1];
[2]Integrative Physiol. and Neurosci., [1]Washington State Univ., Pullman, WA; [3]Univ. of Wyoming, Laramie, WY

**Abstract:** The increasing prevalence of cannabis use in the United States highlights the need for a deeper understanding of its effects. This study explores the hypothesis that cannabis exerts its influence on prefrontal cortex (PFC) activity by modulating the function of parvalbumin positive (PV+) neurons through its impact on perineuronal nets (PNNs).PNNs have been recognized as key regulators of neuronal excitability and intrinsic properties on PV+ neurons. Prior studies have shown that intraperitoneal administration of THC resulted in reduced PNNs associated with PV+ interneurons in male periadolescent rats. However, the influence of sex on PNNs and

cannabis use remains unclear. Work from our group has shown female rats consistently self-administer more cannabis vapor than male rats regardless of age and strain suggesting that sex and sex hormones may be playing a role in cannabis self-administration (CAN-SA). Estradiol and testosterone, key sex hormones, have been implicated in PNN regulation. However, no study has investigated the combined effects of sex hormones and cannabis use on PNN regulation. To address this gap, male and female Sprague Dawley rats (PND 60)underwent castration (gonadectomy in males, GDX; and ovariectomy in females, OVX)with or without hormone replacement (GDX+ or OVX+), or sham surgery, and were trained to self-administer whole plant cannabis vapor. Following CAN-SA, rats were euthanized and analyzed using immunohistochemistry for PV and *Wisteria floribunda* agglutinin, a commonly used PNN marker. Consistent with prior findings, females exhibited higher CAN-SA than males ($p<0.0001$). Preliminary results indicate that, regarding PNNs, CAN-SA increased WFA intensity in WFA+PV+ neurons within the prelimbic prefrontal cortex in females across all groups (Sham: VEH: 100.0±1.4, CAN:117.2±7.5; OVX: VEH: 84.3±1.5, CAN: 94.6±6.5; OVX+: VEH: 100.3±2.5, CAN:112.6±3.3; $p<0.01$) and ovariectomy resulted in a reduction in WFA intensity, which was rescued with estradiol ($p<0.01$). In the infralimbic prefrontal cortex, ovariectomy led to a decrease in WFA intensity in WFA+PV+ neurons that estradiol did not reverse. Ongoing experiments in males and females will further elucidate the role of sex and hormones in modulating PNNs. These findings currently indicate that cannabis exposure modulates PNNs differentially within the prefrontal cortex. Further investigations are necessary to unravel the functional significance of PNN plasticity in neuronal function and its implications for cannabis-seeking behaviors.

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**Poster**

**PSTR046. Cannabinoids: Behavioral and Neural Mechanisms and Addiction**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR046.05/OO3

**Topic:** G.09. Drugs of Abuse and Addiction

**Title:** Palmitoylethanolamide (PEA) causes a dose-dependent decrease in thalamocortical brain activity: A functional MRI study in awake rats.

**Authors: *S. BALAJI**[1,3], E. RICHTER[4], H. B. BRADSHAW[4], P. KULKARNI[3], C. FERRIS[3], *S. BALAJI[2];
[1]Northeastern Univ., Boston, MA; [2]Northeastern Univ., San Jose, CA; [3]Northeastern Univ. Ctr. for Translational Neuroimaging, Boston, MA; [4]Indiana Univ. Bloomington, Indiana Univ. Bloomington, Bloomington, IN

**Abstract:** Palmitoylethanolamide (PEA) is an endogenous fatty acid amide, belonging to a class of lipid signaling molecules, the N-acylethanolamines (NAEs) that includes the endogenous cannabinoid anandamide (AEA). There are numerous preclinical studies showing PEA is an effective analgesic, anti-inflammatory agent and anticonvulsant in different rodent models. The actual mechanism of action for PEA, i.e. molecular targets, and neural circuits, is unknown. PEA is a promiscuous molecule that impacts multiple signaling pathways. It is thought to have an "entourage effect ", enhancing the levels of AEA by indirectly competing with FAAH the primary enzyme for degrading both NAEs. Functional magnetic resonance imaging in awake animals provides a mean of evaluating the effect of exogenous PEA on global brain activity. Specifically, pharmacological MRI (phMRI) provides a view of the integrated neural circuits that respond in a dose-dependent manner to a test compound. When combined with resting state functional connectivity (rsFC) the key nodes and connections in these circuits can be identified. The present studies were undertaken to characterize or "fingerprint" the functional activity of exogenous PEA on brain activity in awake rats using BOLD imaging. Given the reported behavioral effects of PEA, we hypothesized it would interact with neural circuitry associated with pain, e.g., parabrachial n. periaqueductal gray, ventral posterolateral thalamus as identified in other awake imaging studies on rodents and the anterior thalamus and other key node associated with the genesis of clonic-tonic seizures . PEA affected all of these sites, but to our surprise the drug showed a negative BOLD, inverse dose response with the lowest dose (1mg/kg) response having the greatest increase on negative BOLD changes across much of the brain. This response is interpreted as a decrease in brain activity.

**Disclosures: S. Balaji:** None. **E. Richter:** None. **H.B. Bradshaw:** None. **P. Kulkarni:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ekam imaging. **C. Ferris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ekam imaging. **S. Balaji:** None.

**Poster**

**PSTR046. Cannabinoids: Behavioral and Neural Mechanisms and Addiction**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR046.06/OO4

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** VA BX004727-01

**Title:** Cannabis use changes conditioned stress responses by altering the tetrapartite synaptic plasticity in the nucleus accumbens core

**Authors: *R. HODEBOURG**[1], A. TESTEN[1], P. W. KALIVAS[2];
[1]Neurosci., Med. Univ. of South Carolina, Charleston, SC; [2]Med. Univ. S Carolina, Med. Univ. S Carolina, Charleston, SC

**Abstract:** The increasing legal status of cannabis and the high comorbidity between cannabis use disorder and post-traumatic stress disorder (PTSD) creates a need to understand how stress and cannabis interact in the brain. Although the use of cannabis has been suggested to self-medicate PTSD, the literature is mixed on whether cannabis improves or aggravates PTSD symptoms. Using acute restraint stress combined with a rat cannabis self-administration paradigm, I recently found that cannabis use promotes two primary PTSD-like symptoms, avoidance coping behaviors and the generalization of stress-coping responses to a neutral stimulus not previously associated with stress exposure. These changes were accompanied by a reduction in spine density in the nucleus accumbency core (NAcore) and a further decrease in spine head diameter after exposure to the stress-conditioned stimulus (stress-CS). Here we sought to determine whether stress and cannabis exposure also affects matrix metalloproteinases (MMPs), and the perisynaptic astroglial processes. For this purpose, male rats were restraint stressed for 2h and simultaneously exposed to an odor that became the stress-CS. Control rats were exposed to the same odor in the home cage. Three weeks after acute stress, rats self-administered cannabinoids (delta9-tetrahydrocannabinol+cannabidiol; THC+CBD) or vehicle for 10 days, and the stressed rats consumed more THC+CBD than sham rats. After 10 days of extinction, we evaluated the effect of the stress-CS on MMP-2,9 activity, astrocyte morphology, and coping strategies in a defensive burying task (DBT). To this end, rats were microinjected with FITC-quenched gelatin into the NAcore immediately before 15 min of DBT. In THC+CBD-trained rats, the stress-CS prevented active coping (burying) while increasing avoidant coping (immobility-burying ratio and self-grooming). Moreover, the stress-CS increased MMP-2,9 activity only in THC+CBD-trained rats, and this increase is correlated with avoidant coping strategies. Furthermore, withdrawal from THC+CBD decreased the astroglia-synapse proximity, and reduced the re-association of astrocytes to the synapse during exposure to stress-CS. Additionally, the synaptic proximity by astroglia is positively correlated with the active coping, suggesting that THC+CBD potentially exacerbates stress responses by reducing the astrocyte coverage. These findings will help to identify new targets for regulating PTSD and CUD comorbidity.

**Disclosures: R. Hodebourg:** None. **A. Testen:** None. **P.W. Kalivas:** None.

**Poster**

**PSTR046. Cannabinoids: Behavioral and Neural Mechanisms and Addiction**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR046.07/OO5

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** DA000633
1FI2GM138065-01

**Title:** Revisiting the cannabinoid-opioid interaction hypothesis using conditional CB1 and μ opioid receptor knockout mice

**Authors: H. R. ALTON**[1], O. SOLER-CEDENO[1,2], *Z. XI[1];
[1]Natl. Inst. on Drug Abuse, Baltimore, MD; [2]Natl. Inst. of Gen. Med. Sci., Bethesda, MD

**Abstract:** The roles of the CB1 receptor (CB1R) in cannabinoid effects and the μ opioid receptor (MOR) in opioid effects are well characterized. However, there is growing research interest into the functional interactions between these two receptors, particularly at the cellular level. One hypothesis is that there is a direct interaction between CB1R and MOR, possibly through receptor heterodimers, that affects behavioral and pharmacological responses to cannabinoids and opioids. Although numerous studies support this hypothesis, many others do not. The current study aims to address this discrepancy using conditional CB1R- or MOR-knockout mice. A central hypothesis is that if a direct interaction occurs at receptor level, both receptors should be colocalized on the same GABA or glutamate neurons and selective deletion of one receptor should alter or attenuate pharmacological responses to another. To test this hypothesis, we first examined whether selective deletion of MOR or CB1R from GABA or glutamate neurons alters the classical pharmacological effects of $\Delta^9$-THC (a major psychoactive component in cannabis) or oxycodone (a potent synthetic opioid). We found that conditional MOR deletion from either GABA neurons or glutamate neurons failed to alter $\Delta^9$-THC-induced tetrad (analgesia, hypothermia, catalepsy, and immobility) effects, and conditional CB1R deletion from GABA neurons also failed to alter oxycodone-induced analgesia and hypothermia. These findings do not support the cannabinoid-opioid interaction hypothesis. Using RNAscope in situ hybridization, we found that the majority of cells in the paraventricular area of the thalamus (PVT) are VgluT2-positive glutamate neurons and that CB1R and MOR colocalize in ~30% of all PVT cells. In the nucleus accumbens (NAc) and substantia nigra pars reticulata (SNr), where the majority of neurons are GABAergic, CB1R-MOR colocalization was observed in <10% of all cells. Because we found that most CB1R and MOR mRNAs are expressed in different populations of neurons in the PVT, NAc and SNr, our receptor imaging data also failed to provide solid evidence supporting the CB1R-MOR interaction hypothesis.

**Disclosures: H.R. Alton:** None. **O. Soler-Cedeno:** None. **Z. Xi:** None.

**Poster**

**PSTR046. Cannabinoids: Behavioral and Neural Mechanisms and Addiction**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR046.08/OO6

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** MUSC Dept. of Psychiatry and Behavioral Sciences Chair's Fund
American Psychological Association Division 50, Society of Addiction Psychology

**Title:** Identifying changes in phytocannabinoid and endocannabinoid metabolites in cannabis users utilizing a novel UPLC-MS/MS panel

**Authors: *S. R. HUTTON**[1], L. FORD[1], K. GOTLINGER[1], M. FATH[1], R. TOMKO[2], A. EVANS[1], R. SARANGARAJAN[1];
[1]Metabolon, Inc., Morrisville, NC; [2]Med. Univ. of South Carolina, Charleston, SC

**Abstract:** Cannabinoid signaling plays a crucial role in the regulation of diverse neurological processes. However, the complex interactions between exogenous and endogenous cannabinoids in the human body remain unclear. The endogenous endocannabinoid system (ECS) modulates a broad spectrum of neurological functions, including pain perception, appetite, mood, memory, motor function, and inflammatory responses. Moreover, dysregulation of the ECS has been implicated in the pathogenesis of many disorders such as chronic pain, inflammatory disease, neurological disorders, and cancer. Exogenous phytocannabinoids are a diverse group of bioactive compounds found in Cannabis sativa that have been shown to act as exogenous ligands for the ECS, exerting diverse physiological effects on ECS-regulated pathways. As a result, there is significant interest in exploring the potential therapeutic applications of these compounds for ECS-modulated ailments. However, quantifying cannabinoids and their metabolites present unique challenges due to their low abundance and structural variability. A novel targeted UPLC-MS/MS method based metabolomic panel was developed to investigate the potential relationship between cannabis use and endocannabinoid levels in plasma samples from consenting young adults (age 18-25) diagnosed with cannabis use disorder (CUD) based on DSM-5 criteria. Our analysis measured up to eleven endocannabinoids, fifteen phytocannabinoids, and their associated metabolites. Statistically significant differences were observed between the CUD samples and the control group. As expected, tetrahydrocannabinols including delta 9-THC, delta 8-THC, and CBN, as well as human metabolites 11-COOH-THC and 11-OH-THC, were significantly elevated in the CUD group compared to the control group. Conversely, multiple neurotransmitter-conjugated acyl amide endocannabinoid metabolites were significantly reduced in individuals with CUD. Interestingly, these acyl amides are synthesized by the enzyme fatty acid amide hydrolase (FAAH), which previous studies have shown to be differentially expressed in young adult cannabis users. Therefore, the use of our cannabinoid targeted metabolomics panel reveals for the first time an indirect correlation between plasma levels of phytocannabinoid metabolites and neurotransmitter-conjugated acyl amide endocannabinoids in individuals with CUD. Moreover, our study supports the use of targeted metabolomics in providing novel insight involving phyto- and endocannabinoid signaling.

**Disclosures:** **S.R. Hutton:** A. Employment/Salary (full or part-time); Metabolon, Inc. **L. Ford:** A. Employment/Salary (full or part-time); Metabolon, Inc. **K. Gotlinger:** A. Employment/Salary (full or part-time); Metabolon, Inc. **M. Fath:** A. Employment/Salary (full or part-time); Metabolon, Inc. **R. Tomko:** None. **A. Evans:** A. Employment/Salary (full or part-time); Metabolon, Inc. **R. Sarangarajan:** A. Employment/Salary (full or part-time); Metabolon, Inc.

**Poster**

**PSTR046. Cannabinoids: Behavioral and Neural Mechanisms and Addiction**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR046.09/OO7

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** NIH

**Title:** Relationship between cannabis use during pregnancy and infant temperament at 6-8 months of age

**Authors:** A. JOHNSON[1], S. A. LARSEN[2], S. DAGER[3], ***N. M. KLEINHANS**[3];
[1]Univ. of Washington Sch. of Med., Seattle, WA; [2]Univ. of Washington, Seattle, WA; [3]Dept Radiology, Univ. Washington, Seattle, WA

**Abstract:** Cannabis use has increased dramatically over the last decades. Yet, the impacts of prenatal cannabis exposure (PCE) on infant brain development are not well characterized. To address this gap, we followed cannabis-using and non-using pregnant women prospectively, from their second trimester to 9 months postpartum. All were tested periodically for alcohol, tobacco, and illicit drugs. Cannabis use was tracked via weekly survey during the second and third trimesters. Potency and quantity information were used to calculate mean THC dose (mg). Postnatal behavioral and brain imaging assessments were conducted when the infants were between 6-9 months of age (PCE; n=21, M=8.1, SD=2.1, Control; n=25, M=7.9, SD=1.7). Infant temperament was assessed using the Infant Behavior Questionnaire-Revised (IBQ-R). MRI was performed under natural sleep with COVID safety protocols. An olfactometer presented phenylethyl alcohol, a rose-like pure odorant. Two block design runs were collected with four nine-second odor trials separated by an inter-trial interval (ITI) of 18 s. Quiet BOLD fMRI scans were obtained on a 3T Philips Elition X with a 32-channel head coil (TR/TE=1500/30ms, 2.5 $mm^3$ isotropic, MB=3, SENSE factor=2, 72 dynamics). Data analyses were performed using FSL. Preprocessing included motion correction, brain extraction, band pass filtering, detrending, distortion correction, and registration. A basis function with a hemodynamic response optimized for infants was entered into the GLM. FLAME was used for the correlation contrast and thresholded at $z > 2.3$, corrected. Independent samples t-tests on the IBQ-R factor scores revealed elevated Surgency ($p<.05$) in PCE compared to CON infants, but no differences in Negative Affect or Regulation scores. Secondary linear regression analysis between daily THC and surgency was not significant. However, in male infants, greater THC dose was associated with elevated surgency ($r= .653$, $p<.05$). In addition, we analyzed the relationship between brain activation and surgency. 27 infants, (14 PCE, 13 control) provided valid fMRI data. Higher levels of surgency were associated with lower levels of activation in the anterior insular cortex and right amygdala. Our results provide preliminary insight into potential sex-related relationships between THC exposure during pregnancy and infant temperament. Further longitudinal research with a larger group of infants is necessary to confirm these findings.

**Disclosures: A. Johnson:** None. **S.A. Larsen:** None. **S. Dager:** None. **N.M. Kleinhans:** None.

**Poster**

**PSTR046. Cannabinoids: Behavioral and Neural Mechanisms and Addiction**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR046.10/OO8

**Topic:** G.09. Drugs of Abuse and Addiction

**Title:** The FAAH inhibitor URB597 does not normalize increased anhedonia during cannabinoid withdrawal in Long-Evans rats

**Authors: B. MULHOLLAND**, J. BLANCHETTE, D. M. HAYES, *M. L. ECKARD; Radford Univ., Radford, VA

**Abstract:** Approximately 10-30% of lifetime cannabis users meet criteria for Cannabis User Disorder (CUD). Despite the growing need for CUD therapeutics, FDA-approved pharmacological treatments remain to be developed. The endogenous cannabinoid (endocannabinoid) system has been proposed as a primary target for CUD treatment development, somewhat similar to agonist replacement therapies for nicotine or opioid dependence. The endocannabinoid anandamide (AEA) binds to and activates cannabinoid receptors $CB_1$ and $CB_2$, and is primarily hydrolyzed by the enzyme fatty acid amide hydrolase (FAAH). Published data indicate that URB597, an irreversible FAAH inhibitor, is effective in blocking somatic cannabinoid withdrawal signs in rodents presumably through increased AEA signaling along with other minor endocannabinoids that serve as FAAH substrates. However, the efficacy of FAAH inhibition to normalize changes in emotionality and motivation during cannabinoid withdrawal, which humans often report, remains unknown. Therefore, we tested the efficacy of the FAAH inhibitor URB597 in normalizing disruptions in digging behavior via the marble burying test and sucrose preference of rats during withdrawal from the potent synthetic cannabinoid agonist CP-55,940. Adult male and female Long-Evans rats (postnatal day 150) were trained to consume sucrose water (3% wt/vol) in daily two-bottle choice testing for one week. Then, CP-55,940 (0.4 mg/kg, s.c.) or vehicle (1:1:18; ethanol:Kolliphor:saline) was administered twice daily for 5 days while two-bottle choice testing continued. On Day 6, rats were pretreated with URB597 (5.0 mg/kg, i.p.) or its vehicle (1:2:7; DMSO:Tween80:saline). One hour later, all rats received the $CB_1$ antagonist/inverse agonist rimonabant (1 mg/kg, i.p.) to precipitate withdrawal. Testing began 30 min after rimonabant injection. Following rimonabant administration, CP-55,940-treated rats showed significant reductions in sucrose consumption and sucrose preference. While CP-55,940 treatment did not affect digging behavior as has been previously reported, CP-treated rats displayed diminished locomotor habituation during marble burying testing. Notably, pretreatment with the FAAH inhibitor URB597 did not normalize these withdrawal-induced disruptions in behavior. These data indicate possible low utility of FAAH inhibition for normalizing changes in emotionality and motivation during cannabinoid withdrawal. Furthermore, this study underscores the importance of modeling anxiety-like and depressive-like behaviors when assessing candidate CUD therapeutics.

**Disclosures: B. Mulholland:** None. **J. Blanchette:** None. **D.M. Hayes:** None. **M.L. eckard:** None.

**Poster**

**PSTR046. Cannabinoids: Behavioral and Neural Mechanisms and Addiction**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR046.11/OO9

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** DA000633
1FI2GM138065-01

**Title:** Brain CB2 receptor is a new therapeutic target for treating opioid use disorders: Supporting evidence from a new CB2-KO-eGFP reporter mouse line

**Authors: *O. SOLER-CEDENO**[1,2], H.-Y. ZHANG[3], G.-H. BI[1], H. ALTON[1], E. XIONG[1], P. BHATTACHARJEE[4], Q.-R. LIU[5], M. R. IYER[4], Z.-X. XI[1];
[1]Natl. Inst. on Drug Abuse, Baltimore, MD; [2]Natl. Inst. of Gen. Med. Sci., Bethesda, MD; [3]Natl. Inst. on Mental Hlth., Bethesda, MD; [4]Natl. Inst. on Alcohol Abuse and Alcoholism, Bethesda, MD; [5]NIA/NIH, Natl. Inst. on Aging, Baltimore, MD

**Abstract:** We previously reported that CB2 receptor (CB2R) agonists effectively reduce cocaine, nicotine, and methamphetamine self-administration. However, little is known whether they are also effective in reducing opioid self-administration and reinstatement of drug-seeking behavior. In addition, brain CB2Rs are thought to be mainly expressed in microglia. However, direct evidence demonstrating CB2R expression in microglia is still limited, and growing evidence indicates neuronal CB2R expression in rats and mice. We generated a new CB2-KO-GFP reporter mouse line in which the GFP gene sequence replaced the endogenous CB2R-coding region. Next, we used a GFP antibody and immunohistochemistry to examine CB2R-driven GFP expression in the mouse brain. Lastly, we tested the effects of MRI-2594 (a novel CB2R agonist) on heroin self-administration and reinstatement of drug-seeking behavior in rats and mice. In this new mouse line, we detected a high-density CB2R-GFP signal in midbrain dopamine (DA) neurons and cortical and subcortical glutamate neurons, whereas a weak CB2R-GFP signal was detected in microglia, indicating CB2R expression in both neurons and microglia, but much higher in neurons. Notably, CB2-KO-GFP mice showed higher basal levels of locomotion than their wildtype littermates. Systemic administration of MRI-2594 dose-dependently inhibited heroin self-administration and heroin-triggered reinstatement of drug-seeking behavior in rats and wildtype mice, but not in CB2-KO-GFP mice. In addition, MRI-2594 dose-dependently inhibited intracranial self-stimulation (ICSS) maintained by optical stimulation of midbrain DA neurons in DAT-Cre mice, but it did not alter oxycodone-induced analgesia, as assessed by hot-plate test. Together, these findings suggest that CB2Rs are highly expressed in midbrain DA neurons, and that activation of CB2Rs by MRI-2594 inhibits DA-dependent optical ICSS and heroin self-administration. Therefore, MRI-2594 deserves further research as a new pharmacotherapy for opioid use disorders.

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**Poster**

**PSTR046. Cannabinoids: Behavioral and Neural Mechanisms and Addiction**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR046.12/OO10

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** NIH P30 DA048742

**Title:** Comparing self-administration of a synthetic cannabinoid (WIN55,212-2) in male and female Long Evans rats

**Authors: *A. L. BREWER**, S. M. SPENCER;
Pharmacol., Univ. of Minnesota, Twin Cities, Minneapolis, MN

**Abstract:** Drug dependence develops faster in women versus men for cannabinoids and other drugs, which suggests that sex plays an important role in this process. Here we empirically characterized self-administration, withdrawal, and reinstatement of seeking for a synthetic cannabinoid, WIN55,212-2 (WIN), in adult male and female rats. Following jugular catheterization surgery, rats were trained to press a lever to obtain an infusion of WIN or vehicle. Female rats were given access to 6.25 µg/kg in 100 µl volume infusions over a 2-hour period while male rats were given access to 12.5 µg/kg WIN. Correct lever responses were paired with a light and tone cue, while incorrect responses had no consequences. Following self-administration, withdrawal was allowed to occur spontaneously over four days. One week after the final self-administration session, extinction training began wherein active lever pressing was extinguished by removing drug access and cue delivery. Finally, reinstatement of drug seeking was assessed using cue-, drug-, and yohimbine stress-primed reinstatement with extinction sessions alternating between each test day. Both male and female rats responding for WIN demonstrated discrimination for the active over the inactive lever [Males $F(5, 57)=5.726$, $p<0.05$; Females $F(2,24)=68.56$]. Females pressed the active lever at about the same rate as males despite earning only half the dose. Females responding for WIN showed greater lever discrimination than control rats responding for vehicle [$F(1,16)=5.417$, $p<0.05$], however male rats failed to show this same separation. Withdrawal from WIN administration was evident in both males and females, albeit slightly higher and more prolonged in male rats. Initial extinction of lever pressing was identical in female and male rats. Following reinstatements, females given access to WIN took longer to re-extinguish lever pressing. WIN self-administering female rats pressed the active lever more than saline self-administering controls in all three types of reinstatement. In males, lever pressing was higher following cue and drug primed reinstatement but not following stress primed. These results suggest that sex may play a role in self-administration of cannabinoids as females acquired lever pressing and were slower to extinguish behavior despite being given access to only half the dose of the males. To further investigate this effect, we are comparing these results to ongoing studies in which male and female rats are given access to two identical escalating doses of WIN during acquisition of self-administration.

**Disclosures: A.L. Brewer:** None. **S.M. Spencer:** None.

**Poster**

**PSTR046. Cannabinoids: Behavioral and Neural Mechanisms and Addiction**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR046.13/OO11

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** NIAAA R15AA027909 to ESO
NIDA DA031573 and DA021409 to ZL
NIAAA AA026663 to ZL
NIDA DA 047156 and DA0505045 to SB

**Title:** Cannabinoid type 2 receptor neuro-immune crosstalk following microglia and dopaminergic neuron specific deletion of CB2Rs.

**Authors: *E. S. ONAIVI**[1], B. G. KIBRET[1], A. CANSECO-ALBA[2], A. ROBERTS[1], B. SANABRIA[1], P. PATEL[1], M. F. ZAMORA[1], P. TAGLIAFERRO[3], K. MARTIN[1], S. M. BIERBOWER[4], E. ENGIDAWORK[5], S. F. ALI[6], Z. LIN[7], H. ISHIGURO[8], Y. HORIUCHI[9], G. G. GOULD[10], S. BUCH[11], V. SHARMA[1], Q.-R. LIU[12];
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**Abstract:** CB2 cannabinoid receptor (CB2R) is a component of the endocannabinoidome (eCBome) - an expanded endocannabinoid system (ECS) that plays a role in neuroinflammation. This collaborative research using multidisciplinary approaches from different laboratories utilized a battery of *in-vivo* behavioral tests including traumatic brain injury (TBI) models of CNS function, and *in-vitro* assays of immunoblotting, gene expression profiling, immunohistochemistry and IPSCs, to determine the neuro-immuno-modulatory effects of CB2Rs. CB2R conditional knockout (cKO) mice with deletion of CB2Rs from dopamine neurons, DAT-*Cnr2* and those with deletion from microglia Cx3cr1-*Cnr2* displayed differential phenotypes. DAT-*Cnr2* cKO mice displayed hyper-psychomotor responses and were insensitive to the rewarding effects of alcohol but not to cocaine, whereas Cx3cr1-*Cnr2* cKO mice failed to display hyperactivity but were sensitive to the rewarding effects of alcohol and psychostimulants, and exhibited increased weight gain compared to the DAT-*Cnr2* and wild type (WT) controls. The behavioral effects of cannabidiol a non-psychoactive cannabinoid was evaluated in the cKO, WT and the social interaction tests in BTBR mice model of idiopathic autism that was enhanced in the BTBR mice that are otherwise socially deficient. We report that 1). Neuroinflammation pathways of PI3K/AKT/mTOR, MAP/ERK and NF-kβ were differentially affected by the cell-type specific deletion of CB2R in cerebral cortexes of the cKO and WT mice. 2). CB2Rs in dopamine neurons and microglia upregulated the expression of NLRP3 inflammasone pathway including NLRP3, cleaved-caspase 1, and mature form of interleukin II1β in striatal region compared with the WT controls. 3). Microglia activation using

markers for M1 and M2 states were higher in microglia CB2R cKO mice after lipopolysaccharide (LPS-0-48 hrs) exposure. 4). There was increased expression of proinflammatory cytokines TNF-α, IL-6, IL-1α, and IL-1β in the frontal cortexes of the cKO mice following subacute treatment with 8% alcohol compared to the vehicle treated mice. In summary, we demonstrate that selective deletion of CB2Rs from either dopamine neurons or microglia differentially modifies behavioral effects with biased inflammation signaling pathways. Thus, the CB2 cannabinoid receptor neuroimmune crosstalk could be exploited as therapeutic targets in CNS disorders associated with neuroinflammation.

**Disclosures:** **E.S. Onaivi:** None. **B.G. Kibret:** None. **A. Canseco-Alba:** None. **A. Roberts:** None. **B. Sanabria:** None. **P. Patel:** None. **M.F. Zamora:** None. **P. Tagliaferro:** None. **K. Martin:** None. **S.M. Bierbower:** None. **E. Engidawork:** None. **S.F. Ali:** None. **Z. Lin:** None. **H. Ishiguro:** None. **Y. Horiuchi:** None. **G.G. Gould:** None. **S. Buch:** None. **V. Sharma:** None. **Q. Liu:** None.

**Poster**

**PSTR046. Cannabinoids: Behavioral and Neural Mechanisms and Addiction**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR046.14/OO12

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** Japan Society for Promotion of Science (JSPS) Fellowship for Overseas Researchers (P17388)
Kakenhi Grant-in-Aid for JSPS Fellows (17F17388)
Kakenhi Grant for Scientific Research (21K06399)

**Title:** Inhibition of endocannabinoid catabolic enzymes affects locomotory episode structure in mice

**Authors: *B. M. IGNATOWSKA-JANKOWSKA**[1], A. GURKAN OZER[2], A. KUCK[2], M. J. NIPHAKIS[3], D. OGASAWARA[4], B. F. CRAVATT[4], M. Y. UUSISAARI[2];
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**Abstract:** We have previously shown that selective inhibitors of enzymes responsible for endocannabinoid degradation have bidirectional effects on locomotor activity in mice. We observed that inhibition of Fatty Acid Amide Hydrolase (FAAH) and Monoacylglycerol Lipase (MAGL) caused respectively, inhibition and elevation of locomotor activity. Here we evaluated whether these manipulations also modulate the microstructure of locomotory episodes. We used selective inhibitors of endocannabinoid degradation enzymes (MJN110 and PF3845) to elevate the signaling of 2-Arachidonoylglycerol (2-AG) and Anandamide (AEA), respectively. High-speed, high-resolution marker-based 3D motion capture system (Qualisys) was used to track 3D

trajectories of male C57BL/6 mouse trunk and hind limbs during voluntary open field exploration and vertical climbing tasks (n=10 per group). We found that every locomotory episode (defined by maintained displacement of the mouse at speeds over 40 mm/s) is composed of smaller, 1-2 s activity bouts ("locobouts") during which the mice accelerate and decelerate in a repetitive fashion. Unlike highly variable locomotory episodes, the duration of the locobouts and intervals between them was remarkably invariant regardless of treatment and other experimental conditions. Thus, while PF3845 (30 mg/kg) significantly decreased the total number of locomotory episodes compared to vehicle ($p=0.013$) and MJN110 ($p=0.0026$), and increased the length of pauses between them, it did not affect the duration and intervals of locobouts. However, PF3845 caused a significant decrease in the acceleration of the locobouts ($p<0.001$). In contrast, locobout properties were unaffected by MJN110 (2.5 mg/kg), despite a significant increase in number of locobouts per locomotory episode ($p<0.05$). Interestingly, the slight activity-suppressing effect of a well-known cannabinoid receptor agonist CP55,940 (0.3 mg/kg) was accompanied by an increase in the duration of pauses between locomotory episodes without affecting acceleration and duration of the locobouts or their intervals. Our results indicate that the number of locomotory episodes reflects the overall locomotor activity level, while the microstructure of locomotory behavior remains unchanged. The changes in the locomotory episode structure can provide valuable information about the mechanisms underlying observed behavioral effects.

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**Poster**

**PSTR046. Cannabinoids: Behavioral and Neural Mechanisms and Addiction**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR046.15/OO13

**Topic:** B.04. Synaptic Transmission

**Support:** NIH Grant 1R15DA049260-01A1

**Title:** Short-term THC exposure abolishes CB1-dependent ltd in VTA GABA neurons of young, but not adult mice

**Authors: *M. VON GUNTEN**[1,2], S. HOFFMAN[3], D. ISEMONGER[1], A. AVILA[1], J. G. EDWARDS[3];
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**Abstract:** Ventral tegmental area (VTA) dopamine (DA) signaling plays a key role in reward and drug dependence. VTA DA cell activation is regulated and inhibited in part by local GABA interneurons. 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 of young

mice, induced via high frequency stimulation (HFS). This LTD is dependent on metabotropic glutamate receptor 5 (mGluR5) activation and 2-acylgylcerol (2-AG) production. Interestingly, while adults continue to express both functional CB1 receptors and mGluR5-mediated synaptic depression, they require a doubling of the HFS protocol (2x HFS) to induce LTD, and thus adult plasticity is quantitatively different from plasticity in young mice. Because adolescents are more susceptible than adults to the cognitive and addictive effects of THC, we sought to understand age-dependent differences in VTA GABA cell plasticity altered by THC. Therefore, we examined the impact of THC on plasticity in adults versus adolescents using *ex vivo* whole cell electrophysiology in VTA transverse brain slices with extracellular stimulating electrodes after *in vivo* THC exposure. We previously reported that following chronic (7 days) Δ9-tetrahydrocannabinol (THC) injections, LTD is eliminated in both young or adult mice, while a single day of THC exposure does not affect LTD in either 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 effected by age. Thus we treated young and adult mouse with THC for only 3 days, after which we attempted to induce LTD ex vivo. Interestingly, LTD is eliminated after 3 days of THC exposure in young mice ($n = 10$, $p = .107$ compared to baseline), but LTD continues to be present in adult mice ($n = 6$, $p < .001$, compared to baseline). These are also significantly different from each other ($p < .001$). This is the first time that age-dependent differences in drug-induced plasticity in the VTA have been discovered. These findings suggest that age-dependent differences in THC impact on VTA GABA cell plasticity may contribute to the increased vulnerability of adolescents to the negative effects of THC. Currently, we are examining if these age-dependent THC-induced alterations in plasticity correlate with mRNA expression of various endocannabinoid and addiction-related genes using RT-PCR in flow sorted VTA GABA cells. Further research is warranted to explore age-dependent differences in plasticity in other brain areas and cell types.

**Disclosures:** **M. Von Gunten:** None. **S. Hoffman:** None. **D. Isemonger:** None. **A. Avila:** None. **J.G. Edwards:** None.

**Poster**

**PSTR047. Attention I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR047.01/OO14

**Topic:** H.01. Attention

**Support:** NSF Grant 2120539
Searle Scholars Program
NIH Grant NS114191

**Title:** Anticipatory changes in alpha power are associated with suppression of initial afferent activity in human primary visual cortex

**Authors: *C. LI**[1], K. MOHR[2], S. KELLY[2], M. GOMEZ-RAMIREZ[1], I. FIEBELKORN[1]; [1]Univ. of Rochester, Rochester, NY; [2]Univ. Col. Dublin, Dublin, Ireland

**Abstract:** Humans are constantly receiving sensory information from the environment. Because the brain has limited processing resources it deploys a collection of filtering mechanisms to boost the processing of behaviorally relevant information and suppress processing of potentially distracting information. This collection of filtering mechanisms is referred to as selective attention, and has been regularly explored in humans and animals. While there is clear evidence from animal work and human neuroimaging that attention influences sensory processing in primary visual cortex (V1), there remains a debate about whether initial afferent activity in V1 can be modulated by selective attention. One way we can measure initial afferent activity in humans is by the C1, the earliest component in the visual event-related potential (ERP). Due to the retinotopic organization of the striate cortex, in which upper and lower visual hemifields are mapped on the lower and upper banks of the calcarine fissure, respectively, the C1 reverses in polarity depending on upper vs. lower visual-field stimulation. Together with its early onset, typically peaking at 60-90 ms, and repeated source localization, the C1 is considered to index the earliest stages of feedforward processing in V1. Here, we specifically tested whether initial afferent activity in V1—as indexed by the C1 component—is modulated by a well-documented neural marker of selective sensory suppression: increases in alpha-band (8-14 Hz) over areas representing task-irrelevant sensory information. Participants identified targets at a cued location while ignoring stimuli presented at a non-cued location (at the opposite hemifield location). We first replicated previous findings, demonstrating an increase in alpha power contralateral to the cued target location prior to the onset of the target stimulus. We then tested for a relationship between C1 amplitude to unattended stimuli and pre-stimulus alpha power. Our results demonstrate that higher alpha power is associated with a lower-amplitude C1 at the unattended condition (i.e., when a stimulus is irrelevant to the task at hand). These findings provide further evidence from humans that selective attention can modulate initial afferent activity in V1, specifically showing that anticipatory changes in alpha power (i.e., changes occurring during a cue-target delay) are associated with a reduced sensory signal in response to task-irrelevant information.

**Disclosures: C. Li:** None. **K. Mohr:** None. **S. Kelly:** None. **M. Gomez-Ramirez:** None. **I. Fiebelkorn:** None.

**Poster**

**PSTR047. Attention I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR047.02/OO15

**Topic:** H.01. Attention

**Support:** NSF BCS 2022572 to SS

**Title:** Covert attention modulates visual speech perception independent of eye position

**Authors: *K. E. MCEVOY**[1], K. WEGNER-CLEMENS[1], L. E. BERNSTEIN[2], S. SHOMSTEIN[1];
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**Abstract:** Visual information from a speaker's face can help improve speech comprehension, particularly when speech is difficult to understand from auditory information alone (e.g., in a noisy environment). The extent to which visual information aids speech perception differs among individuals, yet the mechanism behind these individual differences is not fully understood. Past research has shown that an individual's visual benefit can be predicted by their gaze position during easy-to-understand speech. That is, even though people tend to shift their gaze to the mouth during noisy speech, not everyone benefits from this shift equally. We hypothesized that differences in covert attention drive individual differences in audio-visual speech integration: individuals who prefer to fixate the eyes may still be covertly attending to the eyes during the noisy speech task even though they are fixating the mouth. To test this hypothesis, participants (n=21) completed a silent vowel identification task during which gaze was fixed to the center of the face (confirmed by eye-tracking), but covert attention was manipulated by an exogenous cue (i.e., a red rectangular box) outlining the eyes or the mouth of the speaker. We observed a strong effect of covert attention, such that when attention (not eye-gaze) was directed to the mouth rather than the eyes, individuals' response times were faster during correct vowel identification ($p = .02$). We additionally measured each participant's visual-only speech perception ability, auditory-only speech ability, and naturalistic eye gaze tendencies during clear speech. A series of mixed effects models showed that these individual difference measures were significant in predicting response times during the silent vowel identification task. The attentional benefit was modulated by individual gaze behavior in free viewing during clear speech, such that individuals who spent more time on the mouth in free viewing were faster on mouth trials. By controlling attention, we have shown that even when fixating the same location on a face, different individuals are covertly attending to and perceiving different information, resulting in different behavioral and likely different neural consequences. It is crucial to better understand individual differences in attention to understand the neural computations that support speech perception.

**Disclosures: K.E. McEvoy:** None. **K. Wegner-Clemens:** None. **L.E. Bernstein:** Other; L. E. Bernstein is a principal of SeeHear LLC, a company that is developing speech perception training. **S. Shomstein:** None.

**Poster**

**PSTR047. Attention I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR047.03/OO16

**Topic:** H.01. Attention

**Support:** Gent university grant: BOF20/GOA/004

**Title:** Investigating the effects of reward motivation on the allocation of feature-based attention

**Authors: *J. O. EAYRS**, C. N. BOEHLER;
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**Abstract:** The allocation of cognitive resources is fundamental to human cognition, and the influence of motivation on this allocation has been a longstanding interest in cognitive neuroscience. It is often assumed that resources, such as visual attention, are limited and that allocating resources to one stimulus results in reduced allocation to others. This being the case, resource allocation is thus thought be to determined by a cost/ benefit analysis based on task demands and anticipated rewards. However, in an influential study using frequency tagged EEG responses to flickering stimuli, Andersen and Müller (2010) demonstrated that attentional enhancement of target features and suppression of distractor features followed distinct time courses, suggesting the involvement of separate cognitive resources. Building upon these findings, we aimed to explore how motivation modulates these distinct aspects of attention using a similar visual attention paradigm: Participants engaged in a visual attention task where two Random Dot Kinematogram (RDK) stimuli, one red and one blue, were presented around fixation. Each of the RDK stimuli were systematically flickered at distinct frequencies (10hz and 12hz), allowing us to track attention allocation to both target and nontarget stimuli via Steady-State Visual Evoked Potentials (SSVEPs). A cue indicated the target color, and participants were instructed to respond to coherent motion in the target dots while ignoring non-target dots. Before each trial, an additional cue indicated the potential bonus reward that could be earned (relatively large or small) for accurate and fast responses. Preliminary results indicate that reward motivation increased attentional enhancement of target-frequency SSVEPs, signifying a greater allocation of attention to these stimuli. However, reward motivation did not result in increased distractor suppression. Instead, we also observed a slight increase in the response to distractor-frequency SSVEPs under high-reward conditions. Furthermore, behavioral data revealed elevated hit and false alarm rates, suggesting that participants adopted a more lenient response threshold when motivated by reward. Further analyses will investigate the temporal dynamics of these effects by examining the time-course of behavior, pupil dilation, and EEG effects. These findings contribute to our understanding of the interplay between reward motivation and attentional processes, shedding light on the nature of resource allocation under reward.

**Disclosures: J.O. Eayrs:** None. **C.N. Boehler:** None.

**Poster**

**PSTR047. Attention I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR047.04/OO17

**Topic:** H.01. Attention

**Support:** NSF Grant SBE2122866
US-Israel Binational Science Foundation Grant #2013400

**Title:** Shifts of object-based attention show a horizontal direction advantage in PPC reflecting limitation on intra-hemispheric exchange of attention information

**Authors: *D. H. HUGHES**[1], A. J. BARNAS[2], A. S. GREENBERG[1];
[1]Biomed. Engin., Med. Col. of Wisconsin, Milwaukee, WI; [2]Psychology, Univ. of Florida, Gainesville, FL

**Abstract:** We have previously shown (Barnas & Greenberg, 2016, 2019), behaviorally, that shifts of object-based attention are asymmetric: there's a horizontal (vs. vertical) shift advantage (the Shift Direction Anisotropy ;SDA) which is larger when shifting attention across the visual field meridians. Here, we used fMRI in 19 healthy volunteers to investigate whether meridian crossing and shift direction modulate attention reorienting signals in posterior parietal cortex (PPC), a critical node controlling attention shifts. We hypothesized that, when subjects shift across the meridians, we would observe differences between horizontal and vertical reorienting signals indicating more efficient reallocation of attention during horizontal shifts (Hughes et al., VSS2022). Subjects were endogenously cued to attend the vertex of an L-shaped object (at one of 2 screen locations) and performed a target detection task with 5 possible target locations: (1) at the object vertex (valid); on the horizontal object arm (invalid-horizontal) at either a (2) near, non-crossing or (3) far, meridian crossing location; on the vertical object arm (invalid-vertical) at either a (4) near, non-crossing or (5) far, meridian crossing location. We used trials from one object location to identify regions of interest in PPC and extracted event-related averages time-locked to target onset for the other object. Results yielded greater activation on invalid (vs valid) trials (4 to 7 s; *t*s > 2.9, *p*s < 0.005) but not during the initial (cue-related) orienting (-4 to -1 s; *t*s < 1.4, *p*s > 0.15), confirming an expected validity effect. A repeated measures ANOVA with crossing condition (crossing, non-crossing), shift direction (horizontal, vertical), and time (4, 5, 6, 7 s) as within-subjects factors revealed all significant main effects (crossing condition: $F(1, 18) = 30.0$, $p < 0.001$; shift direction: $F(1, 18) = 8.1$, $p < 0.005$; time: $F(3, 18) = 32.9$, $p < 0.001$). The crossing X shift direction interaction was also significant, $F(1, 18) = 4.9$, $p = 0.028$. Post-hoc comparisons revealed greater activation during all crossing trials (vs. non-crossing), $t(18) = 2.5$, $p = 0.023$, $d = 0.67$. However, no crossing trial timepoints showed a significant difference between horizontal and vertical shifts (all *p*s > 0.60). Thus, while meridian crossing condition influenced PPC, there was no difference between horizontal and vertical reorienting across the meridians. We, therefore, conclude that the SDA arises not from a shift direction bias in PPC but, instead, via a more efficient exchange of information between (vs. within) hemispheres during horizontal (vs vertical) shifts, reflecting attentional resource limitations.

**Disclosures: D.H. Hughes:** None. **A.J. Barnas:** None. **A.S. Greenberg:** None.

**Poster**

**PSTR047. Attention I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR047.05/OO18

**Topic:** H.01. Attention

**Support:** National Science Foundation of China (31730038)

**Title:** Goal-directed attention transforms target representations in the parietal cortex

**Authors: *H. HU**, G. XUE;
Beijing Normal Univ., Beijing, China

**Abstract:** Attention plays a critical role in determining what to encode into memory, by focusing our cognitive resources on target information and ignoring irrelevant distractions. However, little is known about how selective attention could modulate target representations in order to form long-term memory and reduce interference. To address this gap, twenty-seven adults (11 males, aged 21.96±2.53 years old) were recruited to perform a selective attention and memory recognition task in two consecutive days in the scanner. During the selective attention task, participants were instructed to pay attention to the target picture and ignore the non-target picture presented simultaneously according to the attention cues. A surprising recognition test (half old and half new) was conducted the next day. Behaviorally, attention benefited the long-term memory of targets, with higher accuracy and shorter response time compared to the non-target pictures. Using multi-voxel pattern analysis, we found that selective attention enhanced both category- and item-level target representations in the parietal and visual cortex. In addition, proactive attention shifted the regions involved in the item-specific representation, such that significant item-specific pattern similarity was found in the parietal cortex for the targets presented with non-target pictures, whereas item-specific pattern similarity was found in the visual cortex when the targets were presented without distraction. Interestingly, during retrieval, target and distracted pictures presented simultaneously in the attention task (paired pictures) showed lower pattern similarity than non-paired pictures in the parietal cortex. This repulsion of pair-specific pattern similarity was positively correlated with memory performance. These results suggested that attention can enhance the target representations, shift the representations to a more distractor-resistant area such as the parietal cortex, and orthogonalize the pattern to reduce interference from distractors. Our results emphasize the multiplex role of attention in shaping memory representations.

**Disclosures: H. Hu:** None. **G. Xue:** None.

**Poster**

**PSTR047. Attention I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR047.06/Web Only

**Topic:** H.01. Attention

**Support:** PAPIIT-UNAM #IN217221
PAPIIT-UNAM #IA205218
PAPIIT-UNAM #IN202822
CONACYT #1083933

**Title:** Healthy aging: More years are not always synonymous of cognitive decay

**Authors: *E. LÓPEZ-GONZÁLEZ**[1], I. GÓMEZ-GONZÁLEZ[1], U. CABALLERO-SÁNCHEZ[1], Y. HERNÁNDEZ-DUARCA[1], M. ALVA-CAMARGO[1], D. ZENTENO-MORALES[1], Z. ESPINOSA-VALDÉS[1], I. HERNÁNDEZ-GASCA[1], M. MÉNDEZ-DÍAZ[2], Ó. PROSPÉRO-GARCÍA[2], A. RUIZ-CONTRERAS[1];
[1]Facultad de Psicología, [2]Facultad de Medicina, Univ. Nacional Autonoma de Mexico, Mexico City, Mexico

**Abstract:** Attention allows the selection of relevant stimuli whereas it inhibits the processing of irrelevant ones; however, some stimuli fail to be filtered, capturing attention and diverting it from goal-directed behaviour. Attentional competition of stimuli requires two attentional mechanisms: amplification (the selection of the relevant information) and suppression (the inhibition of the irrelevant information). Failure of either of those mechanisms during information encoding has a negative impact on working memory efficiency (WME). Several functional and behavioural changes in cognitive functions such as attention and working memory have been reported while ageing; however, protective factors have been reported to prevent or delay existing age-associated changes in attention and working memory; thus, understanding the mechanisms of cognitive loss and preservation of cognitive abilities is important for the understanding of healthy ageing. The aim of this study was to detect factors that might be associated with the protection of age-related effects on amplification and suppression mechanisms of attention, by means of the duration of eye movements, as well as the working memory efficiency (WME), measured by the inverse efficiency index. Two-hundred and eight 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 for them during the probe phase: Attending faces/ignoring scenes, Attending scenes/ignoring faces; and Passive view condition, where participants only watch images, and they were asked for responding for the direction of an arrow during the probe phase. Participants also reported their years of schooling and completed a cognitive reserve questionnaire, the Montreal Cognitive Assessment. Years of schooling predicted positively the amplification mechanism (duration of attending faces minus duration of passive view), but age did not; whereas age predicted negatively the suppression mechanism (duration of passive view minus duration of ignoring phases). On the other hand, WME for attending faces was negatively predicted by age, and positively predicted by cognitive function and cognitive reserve; whereas for ignoring faces, WME was negatively predicted by age and positively predicted by years of schooling. Thus, our data suggest that cognitive function, cognitive reserve and years of schooling could be protective factors for declining attention mechanisms and WME.

**Disclosures: E. López-González:** None. **I. Gómez-González:** None. **U. Caballero-Sánchez:** None. **Y. Hernández-Duarca:** None. **M. Alva-Camargo:** None. **D. Zenteno-Morales:** None. **Z. Espinosa-Valdés:** None. **I. Hernández-Gasca:** None. **M. Méndez-Díaz:** None. **Ó. Prospéro-García:** None. **A. Ruiz-Contreras:** None.

**Poster**

**PSTR047. Attention I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR047.07/OO19

**Topic:** H.01. Attention

**Support:** National Eye Institute Grant T32-EY-015387
National Institute of Mental Health Grant MH-117991

**Title:** Does volitional attention operate the same across domains? An investigation of willed attention to color

**Authors: *J. NADRA**[1], M. DING[3], G. R. MANGUN[2];
[2]Ctr. for Mind and Brain, [1]Univ. of California, Davis, Davis, CA; [3]Univ. of Florida, Gainesville, FL

**Abstract:** Attention can be guided by either voluntary (top-down) or involuntary (bottom-up) influences. In real-world vision, voluntary attention can be directed by a wide range of influences such as reward, priming, meaning, experience, selection history, and volition. However, cognitive neuroscience studies of voluntary attention do not adequately capture all of these factors. Laboratory studies of voluntary attention have commonly used attention-directing cues, although self-generated, volitional shifts of attention (willed attention) in the absence of external cues are increasingly of interest (Bengson et al., 2014; Nadra et al., 2023). Prior willed attention studies have exclusively focused on neural activity that predicts the intent to shift covert spatial attention, but this has not been investigated in non-spatial attention. In a feature-based attention paradigm, we have investigated whether the pattern of brain electrical activity (EEG alpha, 8-12 Hz) can predict which color will be attended (orange or purple) when participants are presented with the free choice between the options. Behavioral measures indicate that attention is being adequately allocated to the different color options, with reaction time detriments when only the unattended target appears. Using support vector machine decoding on EEG signals, we found significant differences in alpha-band power for when attention was directed to orange vs when attention was directed to purple, demonstrating that there are distinct electrophysiological correlates underlying willed decisions to attend to different colors.

**Disclosures: J. Nadra:** None. **M. Ding:** None. **G.R. Mangun:** None.

**Poster**

**PSTR047. Attention I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR047.08/OO20

**Topic:** H.01. Attention

**Support:** KAKENHI (21K12089), Mext, Japan

**Title:** The unconscious selection bias in temporal order judgment task with tactile stimulation after presentation of numbers.

**Authors: *T. HORAGUCHI**;
Gunma Paz Univ., Takasaki, Gumma, Japan

**Abstract:** Introduction: It is known that presentation of numbers leads spatial attention bias to the left and right space. This is considered to be because the numerical processing in the brain activates the mentally and horizontally aligned number line on the imaginary space (mental number line). The ascending / descending direction of the mental number line is considered to be due to the cultural habit of reading and writing direction (type 1) or finger counting habit (type 2). In temporal order judgement task (TOJT), two stimuli were delivered with time difference and subjects are required to judge the one delivered earlier. The shorter the difference, the more random the judgments become. Previous study using TOJT with visual stimulus after the presentation of numbers showed clear involvement of type 1 mental number line on the task performance. In the present study, the author examined whether TOJT with tactile stimulus on finger after the presentation of numbers shows involvement of type 2 mental number line after presentation of number.
Methods :A total of 39 healthy subjects were participated (mean age: 20.6±2.1). 35 were right-handed, 3 were left-handed and 1 was ambidextrous. Of those, 24 were classified as R-starter (counting from right fingers) and 15 as L-starter (counting from left fingers). In the TOJT, an one-digit number (1, 2, 8 or 9) was presented for 500 msec on a computer monitor and then a pair of tactile stimuli was delivered to the participants' index finger with intervals of 5, 15, 30, 40, 50, 75, 100 and 150 ms. The participants were required to respond by pushing the button below index finger by the finger stimulated first. The entire sequence of events from presenting the number to responding with finger was defined as a trial. Each participant underwent a total of 256 trials. All procedures used in this research were approved by the local ethical committee of Gunma Paz University.
Results: The author analyzed the results in the intervals of 5 and 15 msec only because the grand average of success rates in these intervals were almost chance level (<60%). The rate of response with right index finger was significantly higher if large number was presented in R-starter whereas it was significantly higher if small number was presented in L-starter ($p < 0.05$).
Conclusion: The results strongly showed that TOJT with tactile stimulus on finger after the presentation of numbers shows involvement of type 2 mental number line after presentation of number, suggesting that different types of mental number lines are activated depending on the type of stimulus delivered to the specific space.

**Disclosures: T. Horaguchi:** None.

**Poster**

**PSTR047. Attention I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR047.09/OO21

**Topic:** H.01. Attention

**Support:** N00014-18-1-2069
N00014-20-1-2709
NSF 1625552

**Title:** Representational analysis of human auditory attention in fMRI

**Authors: *W. GUO**[1], W. AN[3], A. L. NOYCE[2], B. SHINN-CUNNINGHAM[2];
[1]Carnegie Mellon Univ., PITTSBURGH, PA; [2]Neurosci. Inst., Carnegie Mellon Univ., Pittsburgh, PA; [3]Div. of Developmental Medicine, Boston Children's Hosp., Harvard Med. Sch., Boston, MA

**Abstract:** Representational similarity analysis (RSA; Kriegskorte 2008) has allowed researchers to characterize a number of cognitive processes, including visual object recognition (e.g Cichy 2014, Kaneshiro 2015) and audiovisual integration (Cecere 2017). Here, we tested whether RSA could be applied to the similarity structures of internal cognitive control states rather than those of external stimuli, using auditory selective attention as our experimental paradigm. On each trial, subjects were presented with a mixture of 4 overlapping syllables. Depending on the condition (21 in total), subjects (N=19) were cued to use spatial attention, non-spatial attention, or passive listening, and, on attention trials, to report the identity of one target syllable from the mixture. fMRI data (TE = 3.48 ms, TR = 650 ms, SMS8, 2.3 mm isotropic,) were collected and preprocessed. Each subject's data were registered into the MNI152 standard space. Trial-wise activation maps were generated using the least-squares separate approach (Turner 2012), fitting a separate general linear model for each subject and each trial. For each subject and region of interest (ROI), we measured dissimilarity between pairs of conditions by training a support vector machine (SVM) with 12-fold leave-one-run-out cross-validation. Anatomical ROIs were drawn from Destrieux (2010); searchlight ROIs had radius 4mm. Within auditory processing regions in superior temporal gyrus (STG), we primarily observed attention trials separated from passive listening, but with minimal difference between spatial and non-spatial attention. In the parietal lobe, along the intraparietal sulcus (IPS) and superior parietal lobule (SPL), we observed much stronger separation between spatial and non-spatial attention, as well as spatial attention separated more strongly from passive listening than was non-spatial attention. Searchlight-level analyses localized these findings more precisely, showing strongest results in posterior regions of STG and inferior portions of SPL, but consistent throughout the IPS. These results are consistent with previous findings that traditionally-construed auditory and visual processing networks respond differently to spatial versus non-spatial auditory tasks (Michalka 2015, 2017, Deng 2019). The RSA approach allows us to characterize the neural representation of internal states even in the absence of stimulus-level differences between conditions.

**Disclosures: W. Guo:** None. **W. An:** None. **A.L. Noyce:** None. **B. Shinn-Cunningham:** None.

**Poster**

**PSTR047. Attention I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR047.10/OO22

**Topic:** H.01. Attention

**Title:** Effect of spatial attention on human visual motion direction-discrimination at iso-eccentric locations

**Authors: *P. SAXENA**[1], S. TREUE[1,2];
[1]Cognitive Neurosci. Lab., German Primate Ctr., Göttingen, Germany; [2]Fac. of Biol. and Psychology, Georg-August-University, Göttingen, Germany

**Abstract:** The stimulus location dependence of visual perceptual performance as a function of polar angle at isoeccentric locations across the visual field is termed performance field (PF). In humans, performance tends to be superior near the lower vertical meridian compared to the upper vertical meridian, and better near the horizontal meridian compared to the vertical meridian. While these differences have traditionally been attributed to sensory factors, several studies suggest that the allocation of spatial attention may also play a crucial role in modulating the PF. The goal of this study was to investigate the intricate interplay between sensory and attentional effects in shaping the PF, using visual discrimination tasks. Firstly, we established performance fields for dynamic stimuli, specifically focusing on direction discrimination thresholds for moving random dot patterns at four iso-eccentric cardinal locations. Subsequently, we explored whether directing focal attention to specific stimulus locations would yield different effects on discrimination thresholds compared to a condition where attention was distributed broadly. To provide a proof of concept, we conducted a pilot study. We observed lower direction discrimination thresholds for targets along the horizontal meridian in comparison to the vertical meridian. But there were no significant differences in discrimination thresholds between the lower and upper vertical meridians. Furthermore, directing spatial attention resulted in more homogeneous discrimination thresholds across the four locations. These results establish the PF for motion direction discrimination performance in humans and its modulation by focused spatial attention.

**Disclosures:** **P. Saxena:** None. **S. Treue:** None.

**Poster**

**PSTR047. Attention I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR047.11/OO23

**Topic:** H.01. Attention

**Title:** Adaptation to Distractors is Different for High and Low-Adaptation to Distractors is Different for High and Low Level Features in Rapid Serial Visual PresentationLevel Features in Rapid Serial Visual Presentation

**Authors: *A. R. KIMATA**[1], B. ZHENG[1], S. CHAMARTHI[2], T. WATANABE[3], W. F. ASAAD[4];
[1]Warren Alpert Med. Sch. of Brown Univ., Providence, RI; [3]Dept. of Cognitive, Linguistic, and Psychological Sci., [4]Neurosurg., [2]Brown Univ., Providence, RI

**Abstract:** Inhibition of distractors is crucial to accurate processing of task-relevant stimuli. Previous work has demonstrated that distractor suppression in goal-oriented paradigms can facilitate performance and that the effect may depend on properties of the distractor stimulus. In the present study, we use a single-stream rapid serial visual presentation (RSVP) paradigm to test how features and experience with distractors within the RSVP stream, termed "fillers", impacts adaptation to task-irrelevant stimuli. Specifically, we investigated whether changing visual features or varying the amount of exposure to fillers impacted task performance. We found that the adaptation response to low- and high-level fillers was different, with high-level feature changes producing negative priming effects. Performance based on exposure to fillers was influenced by two distinct but interacting processes. Based on these results, we propose that adaptation to low versus high-level feature changes in temporal attention uses distinct mechanisms and that distractor suppression and target facilitation interact to influence target identification in an exposure-dependent manner.

**Disclosures:** **A.R. Kimata:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuropace. **B. Zheng:** None. **T. Watanabe:** None. **W.F. Asaad:** 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.; Vivonics, Inc, Biogen Inc.

**Poster**

**PSTR047. Attention I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR047.12/OO24

**Topic:** H.10. Human Learning and Cognition

**Support:** NSF STC Grant CCF-1231216
NSF Project 2124136
NIH grant DP1HD091947
MIT Research Scholars Program

**Title:** Reasoning about social and physical causes engages the left lateral prefrontal cortex in the human brain

**Authors: *R. PRAMOD**, J. CHOMIK-MORALES, L. SCHULZ, N. KANWISHER;
MIT, Cambridge, MA

**Abstract:** Causal reasoning lets us explain the past, predict the future, and intervene effectively on the present. We reason about both physical causes ("The ice made the car skid") and psychological ones ("The clown made the girl laugh"). How is causal reasoning implemented in the brain? Is it one aspect of a system that is also responsible for other cognitive tasks like holding information in working memory, logical reasoning, and planning? Or might causal reasoning instead be implemented in a distinct brain mechanism not shared with other cognitive processes? A third possibility is that causal reasoning recruits domain-specific mechanisms specialized for understanding and predicting physical and social events. Here we tested these three hypotheses by scanning 18 participants with fMRI while they performed a sentence matching task. We used a blocked 2x2 design crossing causal vs. non-causal events and physical vs. social events. In each block of the causal task, participants viewed four phrases each describing causes or effects, arrayed across the top and bottom of the screen respectively. They were asked to sequentially match each cause to the corresponding effect (e.g., "He was late for work" -> "Tom was scolded by his boss"). Each block of the non-causal condition was the same except the phrases on the bottom and top described the same entity: physical objects (e.g., "The brightest object in the sky", "The closest star to Earth") or social agents (e.g., "She educates children", "She works at a school"). 16 out of 18 participants showed higher responses in the left lateral prefrontal cortex (LPFC) to causal compared to non-causal conditions ($p < 0.001$ uncorrected within each participant). We then used half of the data in each participant to identify the causal > non-causal voxels in LPFC and computed response magnitudes for each of the four conditions in held-out data. We found that causal conditions evoked greater responses than non-causal conditions in both physical domain (18/18 participants; average beta: causal = 0.7; non-causal = -0.2; $p < 10^{-6}$) and social domain (17/18 participants; average beta: causal = 0.6; non-causal = 0.1; $p < 10^{-5}$). There was no significant difference in the average response to physical versus social conditions, indicating the domain-general nature of this response. Control analyses show that the selective response to the causal condition is unlikely to reflect linguistic confounds (word count, word length, grade level) or task difficulty. Taken together, our study provides preliminary evidence for the existence of a region specialized for causal reasoning in human left lateral prefrontal cortex.

**Disclosures: R. Pramod:** None. **J. Chomik-Morales:** None. **L. Schulz:** None. **N. Kanwisher:** None.

**Poster**

**PSTR047. Attention I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR047.13/OO25

**Topic:** H.01. Attention

**Title:** Attention: Relationship Between the Reaction Time and Psychological Factors

**Authors: *B. BAYANMUNKH**[1], N. BAT-ULZII[1], A. CHINGISKHUU[1], A. ZORIGTBAATAR[1], T. BATSUURI[1], B. BUMANDORJ[1], O. ZAMBAL[1], T. JADAMBA[1], B.

LKHAGVASUREN[2];
[1]Dept. of Psychology, Brain and mind research institute, Mongolian Acad. of Sci., Ulaanbaatar, Mongolia; [2]Dept. of Psychology, Brain and Mind Res. Institute, Mongolian Acad. of Sci., Ulaanbaatar, Mongolia

**Abstract: Background:** Psychological experiments and research on the cognitive performance are lack in Mongolia. This test is a widely used method in many types of research in psychology and neuroscience. In our study, we were examinedparticipants simple to difficult form of the interactive Stroop test in Mongolian language using a computer-based version. We aimed to investigate the cognitive parameters, and examine their correlationwith psychological outcomes. **Methods:** A sample of 108 working-aged (range 18-55) were randomly selected in equal numbers from urban and rural regions, participated in the research. The study utilized the Stroop test for cognitive parameters, and Big Five personality test, Depression, Anxiety Stress Scale (DASS-21), and Brief COPE as psychological outcomes. The Kolmogorov-Smirnov test was conducted to assess the normality of the distribution of the data, which was found to be nonparametric. **Results:** The analysis revealed regional differences, with individuals residing in rural areas displaying slower cognitive reaction times compared to their urban counterparts. Furthermore, marital status was found to influence cognitive reactivity, as married participants demonstrated decreased cognitive response times compared to unmarried participants. Spearman's rank order correlation analysis indicated an inverse relationship between agreeableness personality traits (Big Five), and incorrect word responses in the stroop test ($r = 0.217$, $p= 0.024$). And indicated an inverse relationship between problem focused coping style, and incorrect word responses in the Stroop test ($r=-.196$, $p=.043$). Comparison of response times and errors with demographic data revealed regional differences in RT_Black ($p<0001$), RT_Color ($p<001$), and RT_Word ($p<0001$). Interestingly, non-anxious (DASS-21) participants' incorrect word responses in the Stroop test were inversely correlated with depression scores measured by the ($r =.316$, $p =.008$). **Conclusion:** This study contributes to the understanding of the relationship between the Stroop test and psychological outcomes in Mongolia. The findings underscore the significance of considering personality traits, coping styles, regional differences, and psychological outcomes, including depression, when examining cognitive parameters in the context of the Stroop test. Further research in this area is warranted to gain a more comprehensive understanding of the cognitive processes and psychological outcomes involved in Stroop test performance.

**Disclosures: B. Bayanmunkh:** None. **N. Bat-Ulzii:** None. **A. Chingiskhuu:** None. **A. Zorigtbaatar:** None. **T. Batsuuri:** None. **B. Bumandorj:** None. **O. Zambal:** None. **T. Jadamba:** None. **B. Lkhagvasuren:** None.

**Poster**

**PSTR047. Attention I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR047.14/PP1

**Topic:** H.01. Attention

**Title:** Eeg based correlates of attention in intracortical bci motor tasks

**Authors: *E. CANARIO**, M. AKCAKAYA, J. COLLINGER;
Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA

**Abstract:** Intracortical brain-computer interfaces (iBCIs) have made great strides in restoring function to people with paralysis. However, these gains have been primarily limited to the laboratory environment, with little research done to examine iBCI performance in real world conditions involving high cognitive load or distractions. We used a dual-task design to challenge cognitive load during iBCI performance. A 36 year old male with tetraplegia due to cervical spinal cord injury used a motor iBCI to control 2D cursor translation+click with and without simultaneously performing an *n*-back (n=1 or 2) auditory working memory task. EEG (g.tec, 16 channels, 256 Hz sampling rate, 1-59 Hz bandpass filter) was recorded to measure neurophysiological correlates of attention including frontal region theta (3-7 Hz) power, which increases with attention, and parietal region alpha (8-12 Hz) power, which decreases with attention. We also quantified sensorimotor rhythm (13-30 Hz beta band) desynchronization during iBCI control. Frequency band power was computed using the first 6 seconds of each trial, normalized to the average power measured during a 2s intertrial interval. Success rates were similar across the three task conditions, however completion times were significantly slower during concurrent 1-back task performance as compared to the iBCI task alone or the 2-back distraction tasks, which were not significantly different from each other. The participant generally reported higher levels of mental effort (scale of 1-10) for test blocks with the n-back test as compared to without, although the difference was not significant. Performance loss in the 1-back condition was accompanied by an increase in frontal theta power compared to normal iBCI control, which may indicate increased attention however we also observed an increase in parietal alpha power compared to both normal control and the 2-back distractor, which typically indicates decreased attention. Increased alpha has been in found some studies during tasks involving high working memory load, auditory stimulation, or fatiguing tasks, all factors which may be responsible for the increased alpha in this study. Beta band desynchronization was strongest during the 2-back distractor, indicating stronger movement-related neural modulation, which may have contributed to the participant's ability to maintain iBCI performance during this condition. These results establish the feasibility of using EEG to measure attention and movement-related neurophysiologic changes during iBCI performance and provide support for further investigation of BCI performance in more complex situations.

**Disclosures:** **E. Canario:** None. **M. Akcakaya:** None. **J. Collinger:** None.

**Poster**

**PSTR047. Attention I**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR047.15/PP2

**Topic:** H.01. Attention

**Support:** NIH R01-DC019394
NSF SMA 1734892

**Title:** Cortical Responses Time-Locked to Continuous Speech in the High-Gamma Band Depend on Selective Attention

**Authors: *V. COMMURI**[1], J. KULASINGHAM[2], J. Z. SIMON[3];
[1]university of maryland, college park, Wheaton, MD; [2]Electrical and Computer Engin., Unviversity of Maryland, College Park, MD; [3]Electrical and Computer Engin., Univ. Maryland, Col. Park, College Park, MD

**Abstract:** Auditory cortical responses to speech obtained by magnetoencephalography (MEG) show robust speech tracking in the high-gamma band (70-200 Hz), but little is currently known about whether such responses depend at all on the focus of selective attention. In this study we investigate differences in high-gamma cortical responses to male and female speech, and we address whether these responses, thought to originate from primary auditory cortex, depend on selective attention. Twenty-two human subjects listened to concurrent speech from male and female speakers and selectively attended to one speaker at a time while their neural responses were recorded with MEG. The male speaker's pitch range coincided with the lower range of the high-gamma band. In contrast, the female speaker's pitch range was higher, and only overlapped the upper end of the high-gamma band. Neural responses were analyzed using the temporal response function (TRF) framework. As expected, the responses demonstrate robust speech tracking in the high gamma band, but only to the male's speech. Responses present with a peak latency of approximately 40 ms indicating an origin of primary auditory cortex. The response magnitude also depends on selective attention: the response to the male speaker is significantly greater when male speech is attended than when it is not attended. This is a clear demonstration that even very early cortical auditory responses are influenced by top-down, cognitive, neural processing mechanisms. Supported by the National Institutes of Health (R01-DC019394) and the (National Science Foundation (SMA 1734892).

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**Poster**

**PSTR047. Attention I**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR047.16/PP3

**Topic:** H.01. Attention

**Title:** Hemifield bias in load dependent activity during multiple object tracking

**Authors: *M. R. MAECHLER**[1], P. J. KOHLER[2], P. CAVANAGH[3], P. U. TSE[1];
[1]Psychological and Brain Sci., Dartmouth Col., Hanover, NH; [2]Dept. of Psychology, [3]Psychology, York Univ., Toronto, ON, Canada

**Abstract:** The difficulty of tracking multiple moving objects among identical distractors increases with the number of tracked targets. Previous research has shown that the number of targets tracked modulates activity in brain areas related to visuospatial attention, giving rise to so-called 'attention response functions.' While the hemifield/hemispheric effects of spatial attention (e.g., hemispatial neglect, hemifield capacity limits) are well described, whether these effects also impact attention response functions was previously unknown. Using functional magnetic resonance imaging, we show that the number of tracked objects modulates activity in a large network of areas bilaterally. Contralateral tracking load significantly covaried with activity throughout the visual system, while both contra- and ipsilateral load significantly influenced activity in the parietal and frontal lobes, specifically the dorsal attention network. Further, some areas were significantly more sensitive to contralateral than ipsilateral load. We replicate findings showing that a diverse set of brain areas contribute to tracking multiple targets and extend the canonical attention response functions to include hemifield bias. Given the hemifield-specific nature of speed and capacity limits to multiple object tracking, we suggest that those areas that show strong hemifield preference may be the source of overall tracking capacity and speed limits.

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**Poster**

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**Program #/Poster #:** PSTR047.17/PP4

**Topic:** H.01. Attention

**Support:** CRC 1436, C04

**Title:** Neural mechanisms of attentional adaptations following errors

**Authors: *J. TEGELBECKERS**[1], T. SCHAAF[1], M. ULLSPERGER[1,2];
[1]Otto von Guericke Univ., Magdeburg, Germany; [2]Ctr. for Behavioral Brain Sci., Magdeburg, Germany

**Abstract:** Goal-directed behavior requires continuous performance monitoring to flexibly recruit the necessary neural resources. These adaptations are presumably orchestrated by a cognitive control network centered in the posterior medial frontal cortex (pMFC) but the mechanisms underlying post-error changes in task-relevant attentional and perceptual areas are only poorly understood.
Here we aimed to investigate the interplay between performance monitoring and visual selective attention. 33 adult human participants performed a new visual attention paradigm (color orientation interference task) while undergoing functional magnetic resonance imaging (fMRI) and pupillometry.
We found that after errors were committed, pupil dilation, as index of attentional effort, as well

as response times were increased. These effects were accompanied by activity in the pMFC and bilateral insula. Moreover, multivariate pattern analyses showed post-error upregulation of visual attention in the bilateral superior parietal lobules and enhanced representations of task-relevant features in visual areas.
Taken together, these results indicate that cognitive control mechanisms mediated by the pMFC allocate attentional resources after errors. These specific adjustments in attention and perceptual processing might contribute to performance improvements and facilitate adaptive behavior following errors.

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**Poster**

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**Program #/Poster #:** PSTR047.18/PP5

**Topic:** H.01. Attention

**Support:** NSF Grant 1632738
NSF Grant 1632849

**Title:** Neural correlates of Object-Based Attention in early visual cortex in a 100% valid exogenous cueing task

**Authors: *T. K. LYTCHENKO**[1], M. R. MAECHLER[2], N. H. HELLER[2], S. SALEKI[2], P. U. TSE[2], G. P. CAPLOVITZ[1];
[1]Cognitive Brain Sci., Univ. of Nevada, Reno, Reno, NV; [2]Psychological and Brain Sci., Dartmouth Col., Hanover, NH

**Abstract:** A central unanswered question in the study of Object-Based Attention (OBA) is whether attention spreads automatically to the entire object (Chen & Cave, 2006) or whether the pattern of results is driven by other non-obligatory factors, i.e. prioritization of target locations (Shomstein & Yantis, 2002). However, virtually all behavioral measures attributed to OBA are based on examining performance on invalid-cue trials, the inclusion of which confounds the assessment of the automaticity hypothesis. A critical test of the hypothesis would be to determine whether or not effects of OBA can be observed in a 100% valid cueing paradigm. In this paper we investigate the obligatory nature of OBA by leveraging the spatial specificity of functional magnetic resonance imaging (fMRI) and the retinotopic organization of the early visual cortex. We aimed to identify potential neural correlates of OBA in the complete absence of invalid trials. Using fMRI, we had participants perform a version of the classic two-rectangle OBA paradigm while simultaneously measuring changes in BOLD signals arising from retinotopically organized cortical areas V1, V2 and V3. In the first half of the experiment, the cue was 100% valid. In the second half, we reduced cue validity to more closely match standard OBA paradigms (runs containing invalid trials). We sorted BOLD signals arising from our regions of interest (roi)

according to their topographic correspondences with the ends of the rectangles in the visual field. We then compared responses in each roi according to where the cue occurred (Cued, Uncued-Same-Object, Uncued-Other-Object location). We replicated this procedure in Experiment 2, but changed the layout of the two rectangles from vertical to horizontal configuration. Critical result: we observed statistically significant effects of OBA in V3 (Experiment 1) and V1-2 (Experiment 2) in both the 100% and runs containing invalid trials. Moreover, the effects of OBA were no smaller in the 100% runs compared to runs containing invalid trials. Conclusion: we see BOLD modulation at the uncued locations consistent with neural correlates of OBA.

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**Poster**

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**Program #/Poster #:** PSTR047.19/PP6

**Topic:** H.01. Attention

**Support:** NS114191

**Title:** Determining the spatial flexibility of distracter suppression in the tactile modality

**Authors: *A. IGNACO**[1,2], N. SERINO[3], M. GOMEZ-RAMIREZ[1];
[1]Brain and Cognitive Sci., [2]Biomed. Engin., Univ. of Rochester, Rochester, NY; [3]Psychology, The City Col. of New York, New York City, NY

**Abstract:** Selection of behaviorally-relevant sensory information is key for accurate recognition and manipulation of objects with the hand. Selective attention plays an important role in this process by enhancing neural signals encoding relevant tactile information, while also suppressing irrelevant information. However, the underlying properties of how active suppression is deployed in the somatosensory system are relatively unknown. In particular, it is unclear whether distracter suppression can be flexibly allocated to selectively suppress distracters impinging on different locations on the hand. Here, we test whether distracter suppression utilizes either a single vs. divided spotlight mechanism to actively suppress distracters in noncontiguous somatotopic areas. To test this hypothesis, we performed a series of psychophysical studies in humans with attended and distracting stimuli delivered to the hand. Attended stimuli were always presented on the medial pad of the middle finger, with distracters either in a flanking vs. non-flanking arrangement. A visual cue indicated to participants the location of distracter(s) on every trial. Attended stimuli were of 200 Hz vibration frequency and 1000 ms duration. Distracters had the same frequency and duration as attended stimuli, but were half the intensity. Participants reported whether they felt an increase or decrease in vibration intensity at the attended location only. The data showed that cueing the distracter location enhanced threshold and perceptual sensitivity functions of behaviorally-relevant stimuli, indicating that suppression

mechanisms can be actively deployed to irrelevant/distracting touch locations. However, we also observed decreased performance in vibration discrimination and increased reaction time for flanking vs. non-flanking distracter trials, suggesting that tactile distracter suppression operates as a single (and not divided) spotlight mechanism. These findings further our understanding of the mechanism underlying the spatial deployment of distracter suppression, and its potential association with the integration of information across fingers when manipulating objects with the hand.

**Disclosures:** **A. Ignaco:** None. **N. Serino:** None. **M. Gomez-Ramirez:** None.

**Poster**

**PSTR047. Attention I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR047.20/PP7

**Topic:** H.01. Attention

**Support:** the NIHR UCLH BRC Deafness and Hearing Problems Theme

**Title:** Microsaccades as a window to auditory attention

**Authors:** ***M. CHAIT**[1], S. ZHAO[2], C. CONTADINI-WRIGHT[1], M. HUVIYETLI[1], K. MAGAMI[1];
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**Abstract:** Microsaccades (MS) are tiny, involuntary eye movements that occur during fixation. They are controlled by a network involving the frontal eye fields and the superior colliculus and are believed to represent the unconscious continuous exploration of the environment. Recent findings, predominantly in vision, suggest that this sampling is affected by the attentional state of the individual: MS incidence reduces during -and in anticipation of- task-relevant events and under high load. Despite the potential wealth of information conveyed by MS, our understanding of how auditory perceptual processes interact with the attentional mechanisms that regulate MS is limited. We report on a series of experiments (each N=~30) in which we investigated how sounds, and listener engagement with sound, affect MS dynamics. We employed various auditory tasks that captured different aspects of auditory attention, including listening effort, bottom-up attentional capture, and selective attention. Our results demonstrate that auditory attention modulates MS dynamics. Specifically, auditory-evoked microsaccade inhibition (MSI; rapid reduction in MS rate) was influenced by bottom-up attentional capture, exhibiting more pronounced effects for perceptually salient events. MS dynamics were also modulated by top-down attention, such that sounds in an attended stream elicited larger MSI than sounds in an ignored stream. In experiments where participants performed a speech-in-noise task, MS rate was specifically modulated at critical points in the sentence (keywords) where attentional demands were highest. A comparison between concurrently recorded MS and pupil dilation (a common index of instantaneous and sustained arousal) indicate that MS rate specifically indexes

the allocation of instantaneous auditory attention - that is distinct from the modulation of arousal indicated by pupil dilation. Overall, these findings uncover the intricate interplay between auditory attention and the attention network controlling MS, establishing microsaccades as a valuable tool for measuring auditory attentional allocation and related deficits.

**Disclosures: M. Chait:** None. **S. Zhao:** None. **C. Contadini-Wright:** None. **M. Huviyetli:** None. **K. Magami:** None.

**Poster**

**PSTR048. Neural Processing of Value for Decision-Making**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR048.01/PP8

**Topic:** H.03. Decision Making

**Title:** Motor system-dependent reinforcement learning in macaque monkeys

**Authors: *F. GIARROCCO**[1], V. D. COSTA[2], B. M. BASILE[2], M. S. PUJARA[2], E. A. MURRAY[2], B. B. AVERBECK[2];
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**Abstract:** Reinforcement learning (RL) refers to learning to maximize reward and avoid punishment. This process relies on the brain's ability to build a value representation of stimuli and actions, and to use this representation to select behaviors that maximize future rewards. The neural computation behind this function is known to be implemented across motivational regions that learn the value of stimuli and define behavioral goals, and motor-related regions which define and learn the actions to achieve those goals. Current theories of RL suggest that a single value representation in the brain drives learning, independently of the motor system involved. Here we present two complementary studies to challenge this current view. In the first study we tested 23 macaque monkeys, including 12 control, 8 amygdala and 3 VS lesion monkeys on two versions of a three-arm bandit task, where choices were made with either the oculomotor (saccade) or the skeletomotor (reaching) system. In both tasks we constantly presented the monkeys with explore-exploit tradeoffs by periodically replacing familiar options with novel options that had unknown reward probabilities. Thus, exploration was required to learn if novel options could lead to increased future rewards. We found that monkeys were less prone to explore and showed better learning with reaching movements relative to when choices were made with saccades. VS lesions caused the monkeys to be more explorative with arm movements and less explorative with saccades, and amygdala lesions reduced the monkeys' ability to discriminate options by reward probabilities only when choices were made with a saccade. These results show that learning reward value associations to manage explore-exploit behaviors is motor-system dependent and suggest that a different value representation might be driving learning in the oculomotor and skeletomotor systems. To test this hypothesis, in a second study we trained a macaque monkey in a two-arm bandit task in which we randomly intermixed blocks of 30 trials that required the monkey to make a choice either with a saccade or a reaching

movement. We confirmed better performance in reaching blocks compared to saccade blocks. We recorded ~2500 neurons from motivational regions, including amygdala and VS, and motor-related areas controlling the oculomotor and skeletomotor systems, including premotor cortex, posterior prefrontal cortex, caudate, putamen, and globus pallidus pars interna. The application of RL models to our data will allow us to investigate whether and how stimulus- and action-values for the two motor systems are differently represented in the brain and make hypothesis on how they drive learning.

**Disclosures: F. Giarrocco:** None. **V.D. Costa:** None. **B.M. Basile:** None. **M.S. Pujara:** None. **E.A. Murray:** None. **B.B. Averbeck:** None.

**Poster**

**PSTR048. Neural Processing of Value for Decision-Making**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR048.02/PP9

**Topic:** H.03. Decision Making

**Support:** ZIA MH002928

**Title:** Attractor dynamics underlying confidence decisions in macaque prefrontal cortex

**Authors: *S. WANG**[1], R. FALCONE[2], B. J. RICHMOND[SEP][1], B. B. AVERBECK[1]; [1]NIMH/NIH, Bethesda, MD; [2]Albert Einstein Col. of Med., Bronx, NY

**Abstract:** Decisions are made with different degrees of consistency, and this consistency can be linked to the confidence that the best choice has been made. Theoretical work suggests that attractor dynamics in networks can account for choice consistency and change-of-mind. In these network models, decisions are made when network activity settles into one of two attractor basins. Change-of-mind and variability in decision making is accounted for by assuming that transient stimuli or noise pushes neural activity from one attractor basin to another. Theoretically, choice consistency and change-of-mind can be explained by the shape of the energy landscape around the attractor basins. When energy landscapes have steep sides and deep basins, corresponding to a high hill between the valleys, decisions will be made consistently, because it is hard to drive activity from one basin to another. However, when energy landscapes are relatively flat and attractor basins are shallow, decisions will be made less consistently, because it is easier to drive activity between attractor basins.
In this work, we provide empirical evidence that the energy landscape around attractor basins in population neural activity in prefrontal cortex reflects choice consistency. We trained two rhesus monkeys to make accept/reject decisions based on pretrained visual cues that signaled reward offers with different magnitudes and delays-to-reward. Monkeys made consistent decisions for very good (high reward, short delay - accept) and very bad (low reward, long delay - reject) offers. However, their decisions were less consistent for intermediate offers of reward and delay. To estimate the energy landscape in the biological network of prefrontal neurons, we analyzed

neural activity in the state space spanned by the firing rates of individual neurons. Guided by dynamical systems theory, we computed the flow field of neural activity by taking temporal derivatives of neural trajectories in the state space, and then empirically reconstructed the neural energy landscape by taking spatial integrals of flow vectors. We observed the emergence of two attractor basins around the time of choice. Moreover, we found empirical evidence that the energy landscape is steeper following offers that led to consistent decisions. Our finding was supported by examining a dynamical system model fit to the neural data. Therefore, we provide neural evidence that energy landscapes predict decision consistency, which reflects decision confidence.

**Disclosures: S. Wang:** None. **R. Falcone:** None. **B.J. Richmond:** None. **B.B. Averbeck:** None.

**Poster**

**PSTR048. Neural Processing of Value for Decision-Making**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR048.03/PP10

**Topic:** H.03. Decision Making

**Support:** NIMH ZIA MH002928
NARSAD Young Investigator Grant 30892

**Title:** Neural circuit dynamics underlying reinforcement learning in the Macaque

**Authors: *H. TANG**[1], R. BARTOLO-OROZCO[2], B. B. AVERBECK[1];
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**Abstract:** Reinforcement learning (RL) is the behavioral process of learning to associate stimuli or responses with gaining and losing positive reinforcers. Recent studies revealed that RL is mediated by a broad set of cortical and subcortical regions, which can be grouped into ventral and dorsal systems. The ventral circuit is critical for specifying behavioral goals by updating and maintaining the value of stimuli, and the dorsal circuit is critical for orchestrating actions to obtain the goals (H. Tang et al., 2022). However, how value-relevant information flows across the ventral circuit during learning of gains and losses has not been examined. To address this question, we simultaneously collected neural activity in the orbitofrontal cortex (OFC, n = 606), ventral striatum (VS, n = 829), amygdala (AMY, n = 1607), and medial portion of the mediodorsal (MD, n = 1035) thalamus from two rhesus macaques using multi-contact silicon probes as they performed a two-armed bandit token reward learning task. In each block of 108 trials, monkeys learned the values of four novel images that led to increases (+2, +1) or decreases (−1, −2) of tokens. The tokens accumulated across trials and were periodically exchanged for drops of apple juice. In each trial, two images were presented, resulting in 6 choice conditions (e.g., +2 vs. -1). The monkeys' behavior was strongly modulated by the number of tokens accumulated and the updating (gaining vs. losing) of tokens after they made a

choice. We fit the monkeys' behavior with a Markov Decision Process (MDP) model that linked tokens to primary rewards. The model predicted the monkeys' choice, and in addition estimated state value, driven by accumulated tokens and trials to cash out. State values were maintained in the neuronal populations of all recorded areas, most strongly in OFC. The neuronal populations in each area also represented token updates. We are currently examining information flow related to value updating within the circuit we recorded, exploring the hypothesis that neural dynamics across the circuit will maintain and update state value information. Our results suggest a distributed representation of state values in the ventral frontostriatal system during RL.

**Disclosures: H. Tang:** None. **R. Bartolo-Orozco:** None. **B.B. Averbeck:** None.

**Poster**

**PSTR048. Neural Processing of Value for Decision-Making**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR048.04/PP11

**Topic:** H.03. Decision Making

**Support:** NIH DP2MH113095
NIH/NIMH R01MH128669

**Title:** Neural correlates of complex deliberation

**Authors: *T. HONG**[1], W. R. STAUFFER[2];
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**Abstract:** Economic decisions rarely have 'correct' responses. Instead, decision makers must deliberate and determine the most valuable option prior to making a choice. Deliberation can be computationally demanding as values are often dependent on combinations of factors including context, alternatives, and internal states. To investigate the psychological and neural processes for managing computationally complex deliberations, we developed the 'knapsack task' based on the eponymous problem from computer science. The objective of each knapsack trial was to select subsets of items presented on a touchscreen in order to maximize juice reward, without exceeding a fixed limit of 0.8 ml. We categorized the animals' solutions according to the proximity to established computer algorithms. The animals exhibited clear signatures of combinatorial reasoning. In both animals, the deliberation times preceding the first selection, and subsequent inter-selection intervals, reflected the number of operations prescribed by the corresponding algorithms at each step. We performed single-unit recordings in the dorsolateral prefrontal cortex (dlPFC). Single unit responses reflected a variety of task-related variables, including as value, deliberation, and constraints. These results provide strong evidence that the animals adapted algorithmic strategies and employed combinatorial reasoning to manage complex deliberations, and begin to reveal the neural substrates for deliberation.

**Disclosures: T. Hong:** None. **W.R. Stauffer:** None.

**Poster**

**PSTR048. Neural Processing of Value for Decision-Making**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR048.05/PP12

**Topic:** H.03. Decision Making

**Support:** NIH DP2MH113095
NIH/NIMH R01MH128669

**Title:** Ambiguity aversion is a persistent feature of non-human primate behavior

**Authors:** A. ALIKAYA[1], ***W. KERKHOFF**[1], C. MASSOT[1], K. ROTHENHOEFER[2], W. R. STAUFFER[1];
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**Abstract:** Uncertainty is an intrinsic factor in most decisions and, therefore, properly managing uncertainty is crucial for making good decisions. Decision theory recognizes different forms of uncertainty, including risk, when potential outcomes and their probabilities are known, and ambiguity, where the probabilities are not known. Human decision makers prefer the certainty of known probabilities to the uncertainty of unknown probabilities, even if that preference is costly. We and others have shown that ambiguity aversion is also detectable in nonhuman primate (NHP) decision makers, thus establishing a model to study the neural basis of ambiguity aversion. Here, we demonstrate that ambiguity aversion is a persistent feature of NHP decisions and that it is influenced by both reward values and information accessibility. Risky gambles were presented via informative visual bar cues: these informative visual cues independently indicated the potential magnitudes and their associated probabilities using a two-dimensional scale, and ambiguity was introduced by masking the probability dimension. Monkeys (n = 3) made gaze-directed choices. As in previous studies, the monkeys were generally risk seeking and their behavior satisfied first and second order stochastic dominance, indicating that the monkeys were making valid economic choices. Ambiguity aversion was observed in all our animals in paired-lottery tasks. The probability of choosing a particular option was diminished when the probability was hidden, compared to when it was explicitly displayed on the screen. The magnitude of this ambiguity aversion was dependent on overall value: the monkeys were more ambiguity averse when the potential rewards were larger. To examine how much the explicit visual information about probabilities drove behavior, we compared choices between options presented to the animals using the 2-dimensional explicit cues and options presented using well-learned fractal cues. The fractals were trained for thousands of trials. Despite that, when the outcomes and probabilities between the gambles were the same, the animals displayed a strong preference for gambles indicated by explicit visual information. This result suggests that information accessibility is a driving factor in ambiguity aversion. Finally, we replicated these experiments in free-moving animals using an in-cage touchscreen system. We found that measured behavioral effects remained stable across the behavioral contexts. Overall, these results

establish a robust behavioral basis for the study of uncertainty in decision-making and the neural basis of subjective probability beliefs.

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**Poster**

**PSTR048. Neural Processing of Value for Decision-Making**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR048.06/PP13

**Topic:** H.03. Decision Making

**Support:** Wellcome Trust
Royal Society
Human Frontier Science Program

**Title:** Graded Representations of Economic Value Across Frontal Cortex

**Authors: *A. MAJUMDAR**, M. FRITSCHE, C. ASHCROFT, L. STRICKLAND, S. BUTT, A. LAK;
Dept. of Physiology, Anat. and Genet., Univ. of Oxford, Oxford, United Kingdom

**Abstract:** Economic decision-making under risk - the process of selecting between options with different values and uncertain outcomes - concerns many aspects of our lives. Past studies have demonstrated representations of economic decision variables across various regions of the frontal cortex. These studies, however, either measured neural signals with coarse spatial and temporal resolution (e.g. using fMRI) or from small neural populations using electrophysiology. Therefore, a detailed understanding of how fine-grained neural signals from various frontal regions contribute to economic decisions is currently lacking. To address this, we devised a visual economic decision-making task in head-fixed mice, akin to those previously used in studies of non-human primates. In each trial, mice had to choose between two simultaneously presented abstract visual stimuli that differed in their magnitude of associated water reward, and reward probability, resulting in choice options with different expected values and risks. We found that mice's choices were sensitive to the expected value of stimuli: mice consistently selected stimuli with higher expected values. Moreover, we observed diverse risk attitudes across mice, from risk seeking to risk averse. The risk attitude of each mouse was largely stable over both short and long time scales: it did not fluctuate as a function of the recent trial history of wins and losses and remained stable throughout several days of testing. We used high-density large-scale electrophysiological recordings to measure neural signals across many frontal regions during the task. Using population decoding, we show that neural signals across various frontal regions encode economic value, albeit with graded strength. We next investigated whether neural responses reflected individual risk preferences and found that trials with the same expected value but different risk were better decodable from neural responses of risk-sensitive mice, which

preferred or avoided risky stimuli, compared to risk-neutral mice. Our work reveals graded representations of economic value across the frontal cortex, and provides a platform for investigating the neural basis of economic decision-making at a large scale with high spatial and temporal resolution.

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**Poster**

**PSTR048. Neural Processing of Value for Decision-Making**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR048.07/PP14

**Topic:** H.03. Decision Making

**Support:** BBSRC
Wellcome Trust
Royal Society
Human Frontier Science Programme

**Title:** Projection-specific prefrontal neuronal signals during economic decision-making

**Authors: *C. A. ASHCROFT**, A. MAJUMDAR, M. FRITSCHE, J. PODLASKI, L. BIJOCH, A. PACKER, A. LAK;
Dept. of Physiology, Anatomy, and Genet., Univ. of Oxford, Oxford, United Kingdom

**Abstract:** The prefrontal cortex (PFC) plays a crucial role in learning and decision-making. Neurons across the PFC exhibit diverse responses reflecting a range of sensory, motor, and cognitive variables relevant to decision-making. However, the organizing principles that give rise to these diverse representations in PFC remain unclear. Past studies investigating the 'projectome' of PFC neurons in mice have identified the dorsomedial striatum (DMS) and claustrum (CLA) as two of the PFC's main subcortical projection targets. DMS has been found to contribute directly to decision-making through its role in action selection, while CLA has been implicated in processes such as attentional control and impulsivity. We hypothesized that the heterogeneity of PFC responses may map onto differences in their downstream projection targets. To test this hypothesis, we combined a two-alternative economic decision-making task, high-density large-scale electrophysiology, and projection-specific optotagging in mice. In particular, we recorded the activity of a large number of neurons across the PFC using Neuropixels probes during the economic decision-making task. We then identified a subset of these PFC neurons as projecting to the DMS or CLA using antidromic optogenetic stimulation of PFC axons in these two downstream regions. Neurons across PFC as well as the subpopulations projecting to DMS or CLA displayed a rich representation of task variables. We highlight two differences among PFC cells depending on their projection targets: first, DMS- and CLA-projecting PFC neurons display a different distribution across PFC subregions, and second, DMS

and CLA-projecting PFC neurons respond to different combinations of task events. Our ongoing analyses seek to further investigate these projection-specific neural signals as well as PFC population signals during economic decisions. Our work bridges the gap between two levels of insights into the neural basis of decision-making: large-scale neural activity and circuit-specific neural signals. In doing so, we are paving the way to a better understanding of the roles PFC circuits play in decision-making.

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**Poster**

**PSTR048. Neural Processing of Value for Decision-Making**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR048.08/PP15

**Topic:** H.03. Decision Making

**Support:** NSF Grant 2004148

**Title:** Adolescent development shapes adaptive generalization during value-based decision-making

**Authors: *C. INSEL**[1], N. BIDERMAN[2], Z. SHEHZAD[1], D. SHOHAMY[2];
[1]Zuckerman Inst., [2]Psychology, Columbia Univ., New York, NY

**Abstract:** Adolescent brain development provides a window of opportunity for learning. A key feature of adolescence is the rapid expansion of knowledge about the world. This growing knowledge provides a scaffold for generalizing any one particular experience to other similar experiences. This allows individuals to integrate multiple separate memories to build an internal predictive model. However, while this process of learning and generalization has been previously studied in adults, it remains unclear how generalization supports value-based inference during adolescence. From childhood to adulthood, connectivity between the striatum and distributed cortical regions strengthens, which may support the developmental emergence of flexible generalization of value. To test this, we designed a reward-based learning task that leveraged object categories as a form of general knowledge. Participants chose between pairs of objects for the chance to receive a monetary reward. Objects were sampled from 33 distinct categories which were, on average, worth different amounts of reward (e.g., balloons = ~80¢, masks = ~20¢), allowing participants to learn the object category value. We tested whether individuals generalized category value to guide decisions when they were presented with novel objects from previously learned categories. To index explicit awareness of the category value structure, participants self-reported category values after learning. We examined age-related differences in participants aged 10 to 25 years-old. Because retrieving and updating category knowledge relies on cortical systems that continue to mature during adolescence, we hypothesized that flexible category generalization would emerge with age. We found that 10-12 year-olds did not use

category value to guide decision making. However, generalization increased with age, and older adolescents and adults were more likely to generalize category value. Surprisingly, although younger adolescents did not generalize category value to guide decision making, they still reported explicit awareness of the category values following the task. This reveals that younger participants learned category value, but they did not generalize this learning to guide adaptive inference. Together, these findings demonstrate that younger adolescents experience a knowledge-behavior gap: they can explicitly express value knowledge but don't apply it to guide value-based decision making. Future work will identify how ongoing brain development supports the emergence of flexible generalization.

**Disclosures: C. Insel:** None. **N. Biderman:** None. **Z. Shehzad:** None. **D. Shohamy:** None.

**Poster**

**PSTR048. Neural Processing of Value for Decision-Making**

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**Program #/Poster #:** PSTR048.09/PP16

**Topic:** H.03. Decision Making

**Support:** NIH Grant 1F31MH130121-01A1

**Title:** Neural instantiation of a dynamic learning rate

**Authors: *A. MAH**, C. GOLDEN, C. M. CONSTANTINOPLE;
New York Univ., New York, NY

**Abstract:** Dopamine is an important neuromodulator that underlies learning from previous experiences. In reinforcement learning accounts, dopamine is thought to encode reward prediction errors, or the difference between experienced and expected reward, in order to update a recency-weighted running average of previous outcomes to predict future rewards and adjust behavior accordingly. A parameter in reinforcement learning models called the learning rate determines the temporal integration window, with a faster learning rate integrating over fewer trials in the past. Importantly, these models assume a fixed recency weighting (i.e., a static learning rate). We used high-throughput training to collect well-powered datasets from hundreds of rats (N=240) performing a temporal wagering task with semi-observable states (blocks of large or small rewards) distinguishable only by their reward statistics. We found that rats modulated how quickly they initiated trials using previous rewards. However, around hidden-state transitions, when state uncertainty was high, rats integrated over a shorter window (1-2 trials back) compared to periods of low state uncertainty (7-8 trials back), so that rats can more quickly adjust to the new state. Using computational modeling, we found that this behavior was well-described by a model that integrates over previous trials using a dynamic learning rate that changes in proportion to estimated state uncertainty. Finally, to validate the uncertainty-based dynamic learning rate, we measured dopamine release in the nucleus accumbens core using fiber photometry and GRABDA sensors. We found that, consistent with an increased learning rate,

phasic dopamine release was enhanced in periods of high state uncertainty relative to trials with comparable reward prediction errors but low uncertainty. Our work provides novel insights into the role of state uncertainty in shaping both behavior and dopamine dynamics.

**Disclosures: A. Mah:** None. **C. Golden:** None. **C.M. Constantinople:** None.

**Poster**

**PSTR048. Neural Processing of Value for Decision-Making**

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Simons Foundation Junior Fellowship
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5T32MH019524

**Title:** Estrogenic gain control of reward prediction errors during reinforcement learning

**Authors: *C. GOLDEN**[1], D. GREWAL[3], A. MAH[2], T. YAMAGUCHI[4], D. LIN[5], C. J. AOKI[2], C. M. CONSTANTINOPLE[1];
[2]New York Univ., [1]New York Univ., New York City, NY; [3]New York Univ. Ctr. For Neural Sci., New York City, NY; [4]New York Univ., New York Univ. Neurosci. Inst., New York City, NY; [5]New York Univ. Neurosci. & Physiol., New York Univ. Neurosci. & Physiol., New York City, NY

**Abstract:** Despite the broad influence of gonadal hormones throughout the brain, little is known about how these hormones influence cognitive behaviors and their underlying neural substrates. Exogenous estrogenic hormones are known to modulate dopamine signaling in the nucleus accumbens, which is thought to instantiate reward prediction errors (RPEs) for reinforcement learning, raising the intriguing possibility that hormones might influence reinforcement learning. Here we show that endogenous estrogenic hormones that fluctuate over female rats' reproductive cycles enhance reinforcement learning by increasing the dynamic range of dopamine signaling in the NAcc, producing a multiplicative gain on RPEs. We trained rats to perform a temporal wagering task with different reward states. Rats adjusted how quickly they initiated trials across states, balancing effort against expected rewards. In fertile stages, females showed greater sensitivity to reward states, which we show is driven by enhanced encoding of dopamine RPEs

in the NAcc that increase or decrease the perceived value of the environment. During fertile stages, dopamine transporters were reduced in expression, and computational modeling showed that reduced reuptake could increase the gain of RPEs. Preliminary data suggests that genetic suppression of estrogen receptors in midbrain dopamine neurons eliminates hormonal modulation of behavior. Thus, estrogenic hormones control the rate of reinforcement learning by regulating dopamine reuptake, providing a mechanism by which hormones influence neural dynamics for motivation and learning.

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**Poster**

**PSTR048. Neural Processing of Value for Decision-Making**

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**Topic:** H.03. Decision Making

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McKnight Scholars Award
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NSF CAREER (DP2MH126376)

**Title:** Characterizing the dynamics of long-range corticostriatal projection neurons from the lateral orbitofrontal cortex during decision-making

**Authors: *M. L. DEMAEGD**, C. M. CONSTANTINOPLE;
Ctr. for Neural Sci., New York Univ., New York, NY

**Abstract:** Frontal cortical neurons often have complex responses and have been shown to encode multiple task-relevant variables in cognitive paradigms. This complexity may be a core feature of the frontal cortex and indicate that neuronal representations of task-relevant variables are encoded at the level of the population, instead of by individual neurons or subpopulations. However, it remains unclear whether downstream circuits sample from sufficiently diverse frontal cortical neurons to adequately interpret complex population dynamics. An alternative possibility is that downstream brain regions receive only a subset of cortical responses, such that individual task-relevant variables are encoded by subpopulations of frontal cortical projection neurons.
We performed anatomical tracing using fluorescently conjugated cholera toxin subunit B (CTB-Alexa488 and CTB-Alexa647) of corticostriatal projection neurons from the lateral orbitofrontal cortex (lOFC) to the dorsolateral (DLS) and ventral (VS) striatum. We found that projections to these functionally distinct regions of the striatum are composed of non-overlapping populations of neurons located in different layers of lOFC. To characterize the task-relevant dynamics of these subpopulations, we have used viral methods to express channelrhodopsin in projection-

specific neurons. We combined optogenetic stimulation of DLS or VS axon terminals and Neuropixels probes in the lOFC to identify projection-specific neurons on the basis of short latency (10.54±5.4ms), low jitter (1.70±1.17ms) antidromically activated action potentials as rats perform a rich temporal wagering task our lab has developed. We present our evidence for identifying antidromically activated neurons, and preliminary findings of their task relevant responses.
We have also identified other neurons with much longer latency responses or even inhibition following antidromic activation of corticostriatal projection neurons, providing insight into the larger network connections these neurons have within the lOFC. Interestingly, neurons inhibited following optogenetic stimulation show consistent responses to task events, suggesting that striatal projection neurons might inhibit functional cell classes with shared task-relevant responses. Altogether, these experiments hold promise for revealing the circuit logic by which projection-specific subpopulations interact within the OFC and ultimately route information to downstream circuits.

**Disclosures: M.L. DeMaegd:** None. **C.M. Constantinople:** None.

**Poster**

**PSTR048. Neural Processing of Value for Decision-Making**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR048.12/PP19

**Topic:** H.03. Decision Making

**Title:** Striatal dopamine encodes movement and RPE at distinct timepoints

**Authors: *H. JANG**[1], A. MAH[2], C. M. CONSTANTINOPLE[3];
[1]New York Univ. Ctr. For Neural Sci., New York, NY; [2]New York Univ., New York Univ., Queens, NY; [3]Ctr. for Neural Sci., New York Univ., New York, NY

**Abstract:** Midbrain dopamine (DA) neurons are thought to be critical for reinforcement learning and motor control. One important target for DA neurons is the striatum where different subregions are innervated by different midbrain DA neurons. A great deal of evidence suggests that DA release in the ventral striatum acts as a reward prediction error (RPE) while DA manipulations in the dorsolateral striatum produce gross effects on movement. The dorsomedial striatum (DMS), located between the ventral and dorsolateral striatum, may represent an intermediate position along the continuum of value to action coding in the striatum. To address how value and action are represented by DA in DMS, we trained rats on a novel value-based decision making task that includes reward-and motor-related components at distinct points in time that facilitates relating DA to different aspects of behavior. Fiber photometry measurement of DA release in DMS reveals that only some event-aligned phasic DA signals are accompanied by movement, the amplitude of which predicts the vigor of the upcoming contralateral movement. Phasic DA in the absence of movement signals RPE by conveying reward magnitude and probability. Chemogenetic inhibition of DMS impaired rats' ability to adapt their choices

depending on the current reward context. To address which aspect of value processing is impaired, we simulated behavioral data with a Bayesian-inference-based model with softmax policy. We find that the qualitative features of inactivation data are captured by a high softmax parameter, suggesting that DMS inactivation renders policy more explorative. These data suggest that the heterogeneous DA signal in DMS supports value-based decision-making by promoting movement and learning at distinct timepoints for action policies.

**Disclosures: H. Jang:** None. **A. Mah:** None. **C.M. Constantinople:** None.

**Poster**

**PSTR048. Neural Processing of Value for Decision-Making**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR048.13/PP20

**Topic:** H.03. Decision Making

**Title:** Choice Encoding in Rodent Orbitofrontal Cortex

**Authors: *E. CAPEK**[1], S. SCHIERECK[1], A. WILLIAMS[1,2], C. CONSTANTINOPLE[1]; [1]New York Univ., New York, NY; [2]Flatiron Inst., New York, NY

**Abstract:** Orbitofrontal cortex (OFC) is a key structure involved in decision making. OFC is known to represent information about the value, effort, and likelihood of success of various options. However, it is unclear whether this information is used prospectively, to advise future decisions, or retrospectively, to learn from past outcomes. To study the nature of choice coding in OFC, we train rats to perform a temporal wagering task in which they must decide the optimal time to wait for a reward. We record neural dynamics in lateral OFC as the animals perform this task. Here we present evidence that rodent OFC encodes information about decisions before the choices are made. Further, we identify robust cell categories with dynamics which predict the oncoming decision with high accuracy. These findings support the hypothesis that OFC plays a causal role in decision making.

**Disclosures: E. Capek:** None. **S. Schiereck:** None. **A. Williams:** None. **C. Constantinople:** None.

**Poster**

**PSTR048. Neural Processing of Value for Decision-Making**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR048.14/PP21

**Topic:** H.03. Decision Making

**Support:** NIH Grant R01MH125571-01

**Title:** Orbitofrontal cortex supports inference through representations of subjective belief distributions

**Authors: *S. SCHIERECK**, A. MAH, C. M. CONSTANTINOPLE;
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**Abstract:** Orbitofrontal cortex (OFC) has been implicated in myriad aspects of value-based decision making. However, the precise role of OFC in value-based decision making is still unknown. We trained rats on a novel temporal wagering task that requires rats to determine how long to wait for a water reward. The amount of time rats are willing to wait for each reward provides an explicit behavioral readout of rats' subjective value for the offered reward volume. Rewards are presented in blocks of trials with different reward distributions. Rats wait longer for the same reward when the opportunity cost, or the expected reward that is given up by continuing to wait, is lower ("low" reward blocks) compared to when it is higher ("high blocks"). Transitions between reward blocks are not cued, creating partially hidden states. Bilateral muscimol inactivation of lateral OFC (lOFC) reduces modulation of wait time by reward state. Rats are slower to adjust their wait times after a block transition when lOFC is inactivated. This suggests that lOFC is necessary to infer the current reward state based on knowledge of the task structure. To generate hypotheses about how lOFC may contribute to inference, we fit a behavioral model that reproduces several aspects of rats' behavior, and includes interpretable parameters that map onto different aspects of the decision-making process. The model uses Bayes' Rule to predict the identity of the current reward state. It includes parameters representing the opportunity cost in each block (which dictates the wait time in different blocks), and a parameter capturing the extent to which rats use an optimal prior, which contains knowledge about block length, transition probabilities, and reward history. Muscimol inactivation systematically reduced the prior parameter, but not other parameters, suggesting that rats use a less informative prior when lOFC is inactivated. Electrophysiological recordings in lOFC and latent variable modeling show encoding of the prior at the level of single neurons and populations. Tensor components analysis reveals groups of cells that fire preferentially for particular prior probabilities over reward blocks. Regression analysis further suggests that neural activity is more strongly modulated by the prior than other correlated variables, including the posterior and identity of the current block. These data suggest that neurons in lOFC represent rats' subjective belief distributions over partially observable states of the environment, thus supporting hidden state inference.

**Disclosures: S. Schiereck:** None. **A. Mah:** None. **C.M. Constantinople:** None.

**Poster**

**PSTR048. Neural Processing of Value for Decision-Making**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR048.15/PP22

**Topic:** H.03. Decision Making

**Support:** U19 NS104648-01

**Title:** Latent behavioral states reorganize decision-making neural dynamics in a prefrontal-striatal circuit

**Authors: *S. S. BOLKAN**[1], J. R. CHO[1], M. SCHOTTDORF[1], A. G. BONDY[1], J. LOPEZ LUNA[3], A. LUNA[1], B. MCMANNON[1], C. A. ZIMMERMAN[1], R. N. FETCHO[1], A. PAN VAZQUEZ[2], L. S. BROWN[2], Y. EL-JAYYOUSI[2], I. R. STONE[2], I. B. WITTEN[2]; [2]Princeton Neurosci. Inst., [1]Princeton Univ., Princeton, NJ; [3]Princeton Neurosci. Inst., Princeton, NJ

**Abstract:** Our behavior is continually shaped by our internal state - a partially hidden variable that influences our perceptions, decisions, and actions. While several approaches have been developed to probe the neural mechanisms underlying such states, such as measuring the influence of pupil dilation or locomotion on sensory processing, our understanding of how internal state reorganizes activity within, and communication between, brain areas to support state-dependent behaviors remains poor. Here, we combine an unsupervised modeling framework that formalizes internal state as a statistical model of behavior (Bolkan, Stone et al 2022; Ashwood, et al 2022) with high-density, multi-region Neuropixels 2.0 probe recordings of the anterior cingulate cortex (ACC) and dorsomedial striatum (DMS) to examine how internal state influences cortical and striatal neural dynamics in mice performing an evidence accumulation decision-making task (Pinto, Koay, et al 2018). We find that even on trials when mouse decision-making behavior is overtly identical (e.g. correct choices toward a leftward goal) neural activity in both ACC and DMS is sufficient to decode the model-derived internal decision-making state of an animal (task-'engaged' or 'disengaged'). Single neuron encoding and population decoding reveal a greater representation of sensory evidence and earlier representation of upcoming choice in both ACC and DMS during the task-engaged state. These state-dependent differences are starker in ACC than in DMS, and also arise earlier in the temporal progression of a trial in ACC than in DMS. Ongoing work is examining how these internal decision-making states reshape the communication of task-relevant information across time, state, and brain area. To date, our work uncovers state-dependent differences in the neural dynamics across multiple brain areas that support decision-making behavior.

**Disclosures: S.S. Bolkan:** None. **J.R. Cho:** None. **M. Schottdorf:** None. **A.G. Bondy:** None. **J. Lopez Luna:** None. **A. Luna:** None. **B. McMannon:** None. **C.A. Zimmerman:** None. **R.N. Fetcho:** None. **A. Pan Vazquez:** None. **L.S. Brown:** None. **Y. El-Jayyousi:** None. **I.R. Stone:** None. **I.B. Witten:** None.

**Poster**

**PSTR048. Neural Processing of Value for Decision-Making**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR048.16/PP23

**Topic:** H.03. Decision Making

**Support:** NIH U19 NS104648-01
C. V. Starr Fellowship

**Title:** Cross-layer interactions and state-dependent remapping in the anterior cingulate cortex during decision-making behavior

**Authors: *R. CHO**, S. BOLKAN, B. WU, T. EILERS, M. SINISCALCHI, S. THIBERGE, I. B. WITTEN;
Princeton Univ., Princeton, NJ

**Abstract:** Anterior cingulate cortex (ACC) is implicated in critical aspects of cognition, including attention, action selection, and task engagement. Similar to other cortical areas, ACC is a layered structure with predominant connections from superficial to deep layers; however, the computational function of this layered organization remains unclear. We performed 2-photon calcium imaging and Neuropixels 2.0 recordings across layers of ACC, while mice performed a spatial navigation-based evidence accumulation task in a virtual reality setup, to ask what information is communicated across layers, and how this cross-layer communication changes with task engagement. Superficial layer neurons (layer 2/3) fired sparsely relative to deep layer neurons (layer 5), and task variables (such as choice, evidence and outcome) were better represented in the deep layer. Moment-by-moment decoding of sensory evidence and choice was highly correlated across layers during the evidence accumulation epochs, more so than that of outcome during the outcome epoch, suggesting preferential communication of decision-related information across layers. Statistical characterization of cross-layer interactions with reduced-rank regression (Semedo et al., Neuron, 2019) and canonical correlation analysis (Steinmetz et al., Nature, 2019) further confirmed that interactions from superficial-to-deep layers are strongest during the evidence accumulation epoch, and that the communication subspace is best aligned to the choice axis. Next, we applied a hidden Markov model with generalized linear model observations (GLM-HMM) to identify spontaneous transitions in task engagement state (Bolkan et al., Nat Neuro, 2022). This revealed remapping of sensory evidence representations across task engagement states, most dramatically in the superficial layers. Ongoing analyses are focused on understanding how this remapping affects cross-layer communication. Altogether, this work demonstrates that decision-related information is preferentially routed from superficial to deep layers within the ACC, and that sensory evidence representations are remapped in the superficial layer across fluctuating levels of task engagement.

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**Poster**

**PSTR048. Neural Processing of Value for Decision-Making**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR048.17/PP24

**Topic:** H.03. Decision Making

**Support:** Chen Graduate Innovator Grant

**Title:** The neural computations underlying context dependent attribute-based valuation of complex stimuli

**Authors: *A. FRANSEN**[1], K. IIGAYA[2], J. P. O'DOHERTY[3];
[1]Caltech, Pasadena, CA; [2]Columbia Univ., New York, NY; [3]Computation and Neural Systems, California Inst. Technol., Pasadena, CA

**Abstract:** Previous research has shown neural representations of stimulus attributes are integrated to compute an overall value judgment. As our goals and needs change we benefit from modulating the value of relevant items, necessitating flexible rather than static value representations. However, it remains unclear how our brain implements this flexible value modulation on an attribute level for complex objects. One hypothesis is that the value of attributes adapt to changing goals while the integration into an overall value judgment remains stable. An alternative possibility is that flexible value computation is accomplished by adapting the integration mechanism while attribute representations remain stable.
To differentiate between these hypotheses, we designed a paradigm that probes participants' (N=35) value judgments on a set of 75 unique clothing items across 3 goal contexts, while we obtained functional MRI data. To extract attributes of these high-dimensional stimuli we collected participant ratings for subjective attributes (e.g. comfort) and used methods from computer vision for objective attributes (e.g. contrast). Behavioral modeling shows that the weights describing how attributes are integrated into an overall value judgment change across contexts. In further support of the prediction that flexible value is driven by changing integration weights, we find that neural activity reflects the encoding of measured attributes rather than representations of attributes in value space. After integration across attributes, the overall flexible value representation is encoded in the medial frontal cortex. Taken together these results suggest that changes in attribute integration underlie flexible value computation.

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**PSTR048. Neural Processing of Value for Decision-Making**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR048.18/PP25

**Topic:** H.03. Decision Making

**Support:** NSF BCS-2219800

**Title:** Comparing the neuronal substrates for action errors and reward prediction errors at the single neuron level in human medial frontal cortex

**Authors: *Z. FU**[1,2], V. MAN[2], C. M. REED[4], J. M. CHUNG[4], J. O'DOHERTY[2], U. RUTISHAUSER[5,4,6,3];
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**Abstract:** We make all kinds of errors in our daily life. Some errors are caused by exogenous events, such as a frozen app or flat tires on the road; some are our own, such as dialing the wrong number because we are distracted by the TV. The former is useful for learning the values of different options while the latter is useful for optimizing allocation of cognitive control resources. The medial frontal cortex (MFC) is one of the key substrates for signaling reward prediction errors (RPEs) as well as action errors. A major open theoretical question is whether RPEs and action errors are detected and signaled by the same or different neural substrate. We propose that action errors, which are signaled by the error-related negativity (ERN), reflects a local process within the MFC that compares a corollary discharge of the executed action with a predicted action outcome generated by action forward models. The RPE, on the other hand, is a result of input from midbrain dopamine neurons to the MFC. If this hypothesis is true, these two types of error signals should involve separate groups of MFC neurons. In this study, we tested this hypothesis by designing a novel task that elicits uncorrelated action errors and reward prediction errors. The task requires a skilled action to obtain reward, generated by two reward sources of different pay out probability. We recorded single neurons in the MFC in 5 patients implanted with hybrid depth electrodes for evaluation for drug resistant epilepsy. Subjects made action errors in ~20% of trials in attempting to reach the chosen option. These errors did not prevent the subjects from learning about the option values and from attempting to choose the more valuable options, thereby allowing reward learning driven by RPEs. We analyzed the encoding of action errors and reward prediction errors (RPE) at the neuronal level. We found that, across the N=109 recorded MFC neurons, ~23% of neurons signaled action errors and ~22% of neurons signaled reward prediction error. Remarkably, there was little overlap between these two groups of neurons. On the population level, these two groups of error neurons support robust decoding of action errors and RPEs. Evoked potentials showed a similar dissociation between action error and RPE coding. These results support our hypotheses that the action errors and RPE are separate signals in the MFC, useful for updating different representations: the former for updating the state of cognitive control, whereas the latter for updating the value of choices in the external world.

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**Poster**

**PSTR048. Neural Processing of Value for Decision-Making**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR048.19/PP26

**Topic:** H.03. Decision Making

**Support:** NIMH R01MH111425
NSF BCS-2219800

**Title:** Dissociable computational mechanisms and neural representations underlying action versus reward learning

**Authors: *V. MAN**[1,2], A. FRANSEN[2,5], Z. FU[8,2], U. RUTISHAUSER[5,6,7,3], J. P. O'DOHERTY[4,2];
[2]Div. of Humanities and Social Sci., [3]Div. of Biol. and Biol. Engin., [4]Computation and Neural Systems, [1]Caltech, Pasadena, CA; [5]Neurosurg., [6]Neurol., [7]Ctr. for Neural Sci. and Med., Cedars Sinai Med. Hosp., Los Angeles, CA; [8]Dept. of Neurolog. Surgery, Univ. of Texas Southwestern Med. Ctr., Dallas, TX

**Abstract:** Real world decisions require not only the ability to learn about the value of choice alternatives but also the acquisition of skills to implement choices and acquire consequent outcomes. However, the computational and neural mechanisms by which the human brain balances learning across reward and action domains remains an open question. Crucially, it is unclear how neural representations of learning signals respective to each domain, reward prediction errors (RPE) and action prediction errors (APE), are specifically configured in regions relevant for both actions and rewards, such as the basal ganglia and frontal cortex. Whether neural substrates of action versus reward dynamics are separable or overlapping in these key regions is particularly important and understudied in ecologically-valid learning contexts where both types of learning are necessary for successful decision-making.
To elucidate the domain generality versus specificity of learning in the brain, we present a new experimental paradigm designed to elicit dissociable reward and action learning signals. Participants (n=34) completed a novel reward learning task while undergoing fMRI scanning. Critically, in order to select the chosen alternative, participants were required to execute a skilled continuous action in a virtual physical system. The task therefore demanded learning the value of the choices as well as how to execute the action necessary to implement choice. Participants indeed learned across both reward and action domains and we found evidence of stereotyped action trajectories, characterized by decreased variance in their continuous actions across trials, emerging over time and predictive of successful action execution. We present a computational model in which distinct reward and action learning mechanisms are integrated into a combined utility to predict choice. Model-based analysis of uncorrelated prediction error signals revealed distinct encoding in bilateral dorsal versus ventral striatum for APEs and RPEs, respectively. While these signals remained spatially separable in mPFC, we found overlapping uncertainty representations across domains in the frontal pole. Our study reveals that the dynamic and intertwined relationship between action and reward learning is supported by both specific and general representations in the human brain.

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**Poster**

**PSTR048. Neural Processing of Value for Decision-Making**

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**Program #/Poster #:** PSTR048.20/PP27

**Topic:** H.03. Decision Making

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NIH Fellowship 5K00NS105204-05

**Title:** Phase-amplitude coupling in human cortical and subcortical structures during value-based decision making

**Authors: *C. OLIVER**[1], A. L. SAMPSON[1], V. SUBRITZKY-KATZ[1,2], E. EMERIC[1], P. SACRÉ[3,6], W. LIPSKI[7], S. MOREIRA GONZALEZ[7], A. DAMIANI[7], J. GONZÁLEZ-MARTÍNEZ[8], S. SARMA[4], V. STUPHORN[1,5], E. NIEBUR[1,5];
[1]The Zanvyl Krieger Mind/Brain Institute, Johns Hopkins Univ., Baltimore, MD; [2]Dept. of Neurosci., Univ. of Pennsylvania, Philadelphia, PA; [3]Inst. for Computat. Medicine, Dept. of Biomed. Engin., [4]Dept. of Biomed. Engin., [5]Solomon Snyder Dept. of Neurosci., Johns Hopkins Univ., Baltimore, MD; [6]Dept. of Electrical Engin. and Computer Sci., Univ. of Liège, Liège, Belgium; [7]Cortical Systems Lab., [8]Dept. of Neurosurg., Univ. of Pittsburgh Med. Sch., Pittsburgh, PA

**Abstract:** Decision making in the real world involves a complex interplay of different environmental factors and internal states. One mechanism that has been proposed to contribute to the orchestration of cognitive processes in the brain is the modulation of the amplitude of high frequency neural oscillations by the phase of low frequency waves, known as phase-amplitude coupling (PAC). PAC is believed to allow coordination between local and global brain activity, and it may act as a gatekeeping mechanism for high frequency oscillations. It may control and direct localized activity during cognitive processes, including decision making. We observed such phase-amplitude modulation in stereo-electroencephalography (sEEG) recordings obtained from human subjects performing two different decision-making tasks. One was based on the card game "War", the other a risky multi-attribute decision task in which patients are asked to choose between two options with different win or loss amounts and probabilities. We have previously (Subritzky-Katz et al. 57th Annual Conference on Information Sciences and Systems (CISS). IEEE, 2023.) reported the modulation of gamma/high gamma (40-200 Hz) amplitude by theta (4-8 Hz) phase during one of our decision-making tasks. Across all subjects for the “War” task, the period immediately proceeding the outcome presentation showed 45 (10.8%) fewer significant channels than the period following the outcome. Across all subjects for the multi-attribute decision task, the period immediately proceeding the outcome presentation showed 13 (3.3%) more significant channels than the period following the outcome. We found, in agreement with previous observations, that this specific type of PAC is associated with the decision-making process. PAC was present in multiple structures involved in decision making, such as the hippocampus, amygdala, and the anterior end (pole) of temporal cortex. Here, we expand this analysis to identify and include spectro-temporally defined parts of the spectrogram that differ significantly between task conditions, for instance between positive and negative outcomes, e.g., when participants won vs. lost virtual (in the War task) or real (in the multi-attribute decision

making task) money. Significant differences in spectral power were assessed on a region-by-region basis using a nonparametric cluster-based procedure to identify specific time and frequency ranges of interest. We then targeted the PAC analysis to those time-frequency ranges to investigate task-related differences in modulation at these specific regions of interest. Additionally, we show the effects of using different sEEG referencing schemes.

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**Poster**

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NIH Fellowship 5K00NS105204-05

**Title:** Correlates of multi-attribute decision making in human intracranial recordings

**Authors: *A. L. SAMPSON**[1], Q. LIU[1], E. EMERIC[1], W. J. LIPSKI[4], S. MOREIRA GONZALEZ[4], A. DAMIANI[4], J. GONZÁLEZ-MARTÍNEZ[4], S. SARMA[2], V. STUPHORN[2], E. NIEBUR[3];
[1]Zanvyl Krieger Mind/Brain Inst., [3]Neurosci., [2]Johns Hopkins Univ., Baltimore, MD; [4]Univ. of Pittsburgh, Pittsburgh, PA

**Abstract:** Real-world decisions typically require the consideration of multiple options, each of which is defined by multiple attributes. To study such multi-attribute decisions, we have implemented a tablet-based task offering participants the choice between two different options. On two thirds of the trials (the “win domain”), both options offered cash rewards of different amounts and with different probabilities. On one third (the “loss domain”) both options resulted in losing money, again with specified amounts and probabilities of losing. Attributes types (amounts and probabilities) are represented by separate symbols and these symbols mask the attribute values which are only displayed (unmasked) when participants click on the respective symbol. Participants can freely select as many times as desired which attributes they view but only one attribute of one option may be inspected at a time. When the participant has come to a decision, they select the chosen option by tapping on a dedicated symbol. This sequence of events gives us the ability to precisely observe when each piece of decision-relevant information is being collected.
To study the neural correlates of this decision process, we collected stereoelectroencephalogram

(sEEG) recordings from patients undergoing treatment for medically intractable focal epilepsy while they performed the multi-attribute decision task (85+/-72 win domain trials and 40+/-36 loss domain trials from 13 patients, mean and standard deviation across patients). Event-aligned spectrograms were computed for the beginning of each trial of the task, the inspection (unmasking) of all attributes of all options, taps on "select" to indicate a chosen option, and the moment when the outcome of the trial is displayed. Spectral power across frequency and time adjacent to these events was then tested with a nonparametric cluster-based test for significant differences depending on task condition, such as: win vs. loss, likely vs. unlikely outcome, amount inspection vs. probability inspection, win domain inspection vs. loss domain inspection. Further, spectral power was tested for significant correlation with task defined variables, such as: inspected attribute magnitude, inspected option expected and subjective value, chosen option expected and subjective value, and win or loss amount. Significantly task-related activity was identified in a range of cortical and subcortical regions, including the orbitofrontal cortex, dorsolateral frontal cortex, mesial frontal cortex, insula, amygdala, and hippocampus.

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**Poster**

**PSTR048. Neural Processing of Value for Decision-Making**

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**Topic:** H.03. Decision Making

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NIH/NIDA grant R01DA040990
ONR grant N00014-22-1-2699
NIH D-SPAN K00 Fellowship

**Title:** Millisecond Timescale Spike Synchrony during Decision-Making in Non-human Primate pre-SMA

**Authors: *S. LOCKE**[1,2], Y.-P. YANG[4], A. SAMPSON[2], E. E. EMERIC[2], M. USHER[5], D. J. LEVY[6], V. STUPHORN[2], E. NIEBUR[2,3];
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**Abstract:** Humans and animals are constantly confronted with complex, value-based decisions which require accurate collection of information about the available options. While there has been progress in understanding behavioral principles underlying multi-attribute decision-making, much less is known about their neural correlates. In macaques, it has been previously suggested

that pre-Supplementary Motor Area (pre-SMA) neurons have a role in updating internally generated motor plans and thus may encode information related to multi-attribute motor decisions. Two macaques were trained to make a motor decision related to risky choice. On each trial, the monkeys were presented with two visual stimuli, corresponding to two options the monkeys could choose from. Each option was characterized by the amount of liquid reward the animal could obtain and the probability of receiving it. Neural activity was recorded from pre-SMA and analyzed during 6 separate periods corresponding to different stages of the task. One of the key periods of interest is the information gathering (IG) period, when animals fixate attributes to gain information about the two options. We find significant millisecond timescale synchrony in the jitter-corrected cross-correlograms (Amarasingham et al, J. Neurophysiol. (2) 517-31, 2012) in 35% (45/127) of pairs when analyzing data across the whole trial (permutation test, $p < 0.01$). When analyzing the six task periods separately, we find strong synchrony in all periods of interest, with the largest number of significant pairs (24) occurring during the IG period, followed by the post-reward period (22) and the pre-Response period (18). Additionally we compared the distribution of the synchrony between the IG period and other trial periods using a jitter-based synchrony index (JBSI; Agmon, Neural Systems \& Circuits 2.1: 1-15, 2012). We find no significant differences in the strength of synchrony in any comparison (Kolmogorov-Smirnov, $p>0.05$). Within the information-gathering period, we observe 20 significant pairs during initial fixations to attributes, compared to 4 significant pairs during repeated fixations to the same attributes. This suggests that millisecond timescale synchrony may encode novel information. These results add to the existing literature suggesting that stimulus and behavior-modulated synchrony supports the cortical organization of cognitive motor processes and decision-making.

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**Poster**

**PSTR048. Neural Processing of Value for Decision-Making**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR048.23

**Topic:** H.03. Decision Making

**Support:** NIH Grant R01-DA032758
NIH Grant R01-MH104494

**Title:** Optimal coding of offer values in orbitofrontal cortex: theoretical predictions and experimental tests

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**Abstract:** A binary economic choice entails the computation and comparison of two offer values. When monkeys chose between different goods, two groups of neurons in orbitofrontal cortex (OFC) encode the two offer values. Importantly, experiments using electrical stimulation demonstrated a causal relationship between the activity of offer value cells and choices. Given a value range, the tuning curves of offer value cells are quasi-linear and independent of the distribution of the offers. The gain of the tuning curves (i.e., the slope of the encoding) is inversely proportional to the value range (range adaptation). In previous work, we developed a theory of optimal coding for offer values (Rustichini et al, 2017). The central concept is that the encoding of offer values is optimal if tuning curves ensure maximal expected payoff (i.e., maximum chosen value). The theory is based on a linear decision model, where choices are determined by the difference between the activity of the two groups of offer value cells. The theory indicates that quasi-linear tuning curves are optimal only if the two value ranges are equal and the joint distribution of offer values is uniform within the relevant domain of offers. (Since this condition is not satisfied in our experiments, quasi-linearity can be viewed as an inflexible trait of the tuning functions, presumably advantageous in an evolutionary perspective.) The theory also demonstrates that, for linear tuning curves, range adaptation ensures maximal expected payoff. Finally, indicating with A and B the two offered goods, with $\Delta VA$ and $\Delta VB$ the two value ranges, and with JA and JB the efficacy of synapses for which offer value A and offer value B cells are pre-synaptic, the theory predicts the relation $JA/JB = \Delta VA/\Delta VB$. We have now generalized this prediction for a decision model that (a) includes the other groups of neurons identified in OFC (encoding the chosen good and the chosen value) and (b) is fully connected. We have also tested the prediction using estimates for the synaptic efficacies derived from network inference analysis (Ising model) applied to populations of 20-120 neurons recorded simultaneously. Preliminary results based on a limited data set support the theoretical prediction. This finding validates the theory and supports the understanding that offer value cells in OFC are optimally tuned for economic choices.

**Disclosures: C. Padoa-Schioppa:** None. **G. Tavoni:** None.

**Poster**

**PSTR048. Neural Processing of Value for Decision-Making**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR048.24/QQ2

**Topic:** H.03. Decision Making

**Support:** ERC Grant RaReMem (ID:101043804)

**Title:** Context distorts value representation across different learning modalities and elicitation methods

**Authors: *M. SOUKUPOVA**, S. PALMINTERI;
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**Abstract:** While the functional form of value encoding has not yet been resolved, it is clear that the perceived value of an object is influenced by the other objects presented simultaneously. Importantly, this value distortion also occurs when stimuli that were initially encountered within a fixed context, i.e. pair, are seen outside of this original context (Bavard et al., 2018). Here we present results of three online experiments (N=287, 129 women) that demonstrate that value distortions remain stable across different learning modalities (experience vs. description) and memory elicitation methods. Furthermore, we show that the direction of these distortions can be predicted from the architecture of the learning task.
In all experiments, participants first completed a learning task where they encountered eight different options presented in fixed contexts. The options differed in valence, magnitude and probability of obtaining a non-zero outcome. Immediately afterwards, participants performed two memory tests. In the implicit test, participants had to select the best option from each possible pairwise combination, while in the explicit test, they had to recall the non-zero outcome of each option.
Participants' responses in the memory tests were used to calculate the explicit and implicit rankings of each option. The rankings were highly correlated with each other and reflected a mix of the option's global rank (compared to all other options) and its local rank (compared to its learning pairmate). This indicates that value encoding is universally distorted. Crucially, the rankings were not affected by the learning modality. While participants who learnt from description exhibited higher learning accuracy compared to those who learnt from experience, their implicit and explicit rankings in the memory tests were qualitatively similar, suggesting that increasing the amount of information given to the participants does not affect value encoding. Furthermore, by manipulating the learning architecture across experiments, we were able to alter the local ranks while keeping the global ranks stable, thereby revealing that both the implicit and explicit rankings change based on the local rank.
We thus demonstrated that the observed value distortion is universal and systematically emerges from learning architectures that favour contextual learning, rather than learning modality or any intrinsic properties of the options themselves, bringing us a step closer to understanding the cognitive mechanisms of value representation.

**Disclosures:** **M. Soukupova:** None. **S. Palminteri:** None.

**Poster**

**PSTR049. Inhibitory Control and Disorders of Executive Functions**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR049.01/QQ3

**Topic:** H.04. Executive Functions

**Support:** NIDA Grant P50DA037844
NIAAA Grant T32AA007583

**Title:** Genome-wide association study in outbred heterogeneous stock rats identifies loci for a reaction time task.

**Authors: *C. KING**[1,2], K. ISHIWARI[2], A. CHITRE[3], O. POLESSKAYA[3], D. DIETZ[4], A. M. GEORGE[2], C. D. MARTIN[2], L. SOLBERG WOODS[5], H. CHEN[6], J. B. RICHARDS[2], A. A. PALMER[7], P. MEYER[1];
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**Abstract:** Addiction vulnerability and compulsive drug-seeking are associated with traits such as attentional control, action impulsivity, and cue-reactivity. To characterize the genetic bases of these traits, we conducted a genome-wide association study (GWAS) in a cohort of 1,612 phenotypically and genetically diverse N/NIH Heterogeneous Stock (HS) rats. HS rats were tested in a reaction time task, in which rats were required to maintain attentional control and respond to a visual stimulus for a water reinforcer. We characterized individual differences in attentional control by measuring reaction time and action impulsivity by measuring incorrect and premature responses during the task. GWAS yielded 22 unique quantitative trait loci (QTLs) across 24 phenotypes. Among the most heritable were reaction time, premature responses, and trial completion ($h^2$ = .19-.22). QTLs identified for reaction time and premature response were located on chromosomes 1, 2, 5 and 14 which varied in interval size and the number of candidate genes within these regions. For example, the QTL for action impulsivity contained *Fancl* and *Vrk2*, both of which were previously identified in human GWAS for smoking (Linnér et al. 2019), depression (Nagel et al. 2018) and antidepressant efficacy (Li et al. 2019). Expression-QTL in mesocorticolimbic regions of the brain revealed both novel candidate genes (*e.g. Sucnr1*, *Myh6*) as well as genes previously implicated in substance use disorders by GWAS in humans (*e.g. Ctsc*, *P2ry12*). Thus, we demonstrate that HS rats are useful for investigating the genetic variants underlying complex behavior and in identifying candidate genes for future testing.

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**Poster**

**PSTR049. Inhibitory Control and Disorders of Executive Functions**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR049.02/QQ4

**Topic:** H.04. Executive Functions

**Support:** University of Rochester Intellectual and Developmental Disabilities Research Center (IDDRC, P50HD103536)
The Schindler Foundation

**Title:** Cognitive-motor interactions in neurotypical children and young adults using mobile brain-body imaging (MoBI) show age-related differences in neurophysiology and response inhibition task performance

**Authors: *P. R. NICKLAS**, J. J. FOXE, E. G. FREEDMAN;
Neurosci., Univ. of Rochester, Rochester, NY

**Abstract:** Cognitive-motor (C-M) interference is a phenomenon during which demands from concurrent cognitive and motor tasks create competition for available neural resources, causing performance decrements in one or both modalities. Research can introduce this competition using dual-task designs to compare performance on single-task situations to dual-tasks, which require both motor and cognitive engagement. However, recently ~50% of a group of young adults (YAs) improved performance on an RI cognitive task when walking, contrasting the idea of C-M interference. The improvers displayed significant differences in neurophysiological and gait profiles, while no differences were observed in non-improvers. This demonstrates that while some individuals experience C-M interference, others have a more integrative effect, presenting as better adaptation to multi-modal demands. Little is known about how this C-M relationship develops, nor what factors play a role in the integration observed in some. Using an RI task to compare ERPs of children and adults, inhibition has been shown to be less widely distributed and more frontally-focused with increased age, but it is unknown how this will present when dual-tasking. To examine this, we use Mobile Brain-Body Imaging, which permits synchronous recording of neurophysiologic (electroencephalography/EEG), kinematic (motion-tracking), and behavioral (task performance) data. This is the first study to use these methods in those < 18 years old. Participants complete a Go/NoGo RI task while sitting and walking on a treadmill. We record a cognitive assessment, physical activity survey, and biometrics. We hypothesize children will display greater C-M interference compared to YAs, evidenced by greater decline in task performance when walking, and lesser EEG differences between motion states. Additionally, the proportion of improvers will be greater in YAs. Preliminary data shows differences in YAs and children between motion states at expected latencies and loci of the event-related potentials (ERPs) N2 and P3. Children's ERP loci have a wider distribution compared to YAs. When walking, children improve their task performance more often than YAs. Behavioral assessments show no significant correlations with change in peak N2 amplitude or task performance when walking, suggesting the differences observed there cannot be related to single modal abilities for either age group. This work hopes to reveal how components of C-M interaction develop and elucidate markers of those who are able to access mechanisms that lead to improvement when dual-tasking. More data collection is needed to compare age groups with suitable power.

**Disclosures: P.R. Nicklas:** None. **J.J. Foxe:** None. **E.G. Freedman:** None.

**Poster**

**PSTR049. Inhibitory Control and Disorders of Executive Functions**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR049.03/QQ5

**Topic:** H.04. Executive Functions

**Support:** Conacyt 812748

**Title:** Sexual differences in brain activity and functional organization during inhibition processing: a Go/NoGo task study

**Authors: *S. P. CAÑARTE VARELA**[1], Y. DEL RÍO PORTILLA[2], I. GALÁN LÓPÉZ[3];
[1]Lab. de Sueño, Univ. Nacional Autónoma De México, CDMX, Mexico; [2]Lab. de Sueño, [3]Univ. Nacional Autónoma de México, Ciudad de Mexico, Mexico

**Abstract:** Differences in brain organization and processing between women and men have been a subject of ongoing debate. Additionally, it has been observed that inhibition processing varies across hemispheres in relation to sexual differences. The present study aims to investigate brain responses during a Go/NoGo task in women and men. Participants were exposed to 150 stimuli (red, blue, and green circles) with a duration of 1.6 seconds each. The stimuli were presented using a classical random block design specific to each gender group. Following each run, participants (n = 21 males, n = 21 females) indicated the location of the stimuli (right or left side) using their dominant hand on a PC keyboard. No response was required for green stimuli. Eye movement data was recorded using electrooculogram (EOG) electrodes. Results revealed significant differences in brain activity between women and men during inhibitory processing. However, an analysis of behavioral data did not yield any significant differences in response patterns. Electroencephalographic activity was used to analyze absolute potential (AP) (p &lt 0.05). Women exhibited higher activity in the Delta, Theta1, Theta2, Alpha1, Alpha2, Beta1, and Total bands during the task. These findings provide evidence supporting the hypothesis of distinct functional brain organizations associated with inhibition processing in women and men.

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**Poster**

**PSTR049. Inhibitory Control and Disorders of Executive Functions**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR049.04/QQ6

**Topic:** H.04. Executive Functions

**Support:** Shanghai Municipal of Science and Technology Project (Grant No. 20JC1419500)
Science and Technology Innovation 2030-Major Project(Grant No. 2021ZD0202202)

**Title:** Nonselective response of chandelier cells in medial prefrontal cortex to behavioral tasks

**Authors: *M. WU**, J. XU, L. LIN, Y. GU;
Inst. of Brain Functional Genomics, East China Normal Univ., Shanghai, China

**Abstract:** The diversity of neuron types poses great challenge to decode neuronal network dynamics, especially the numerous types of cortical interneurons. Chandelier cell(ChC), a GABAergic interneuron with unique morphological characteristics that target the axon initial segments(AIS) of pyramidal neurons, is one of the most fascinating interneuron subtypes in the cortex. However, the *in vivo* electrophysiological (ephys) profile of ChC has long been missing due to technical restrictions. Combining *in vivo* multichannel ephys recording with optogenetic identification, we acquired the long-term *in vivo* firing activities of ChCs in layer II of the medial prefrontal cortex (mPFC) in free moving mice. We found that optogenetic activation of ChCs produced inhibitory effects on a large number of neurons, including pyramidal neurons and interneurons. Firing activities of ChCs are only phase locked to high frequency oscillation (>100 Hz) of mPFC local field potential. This regulation is restricted to the axon spanning range of ChCs. ChCs increased their firing rates with adaptive activity changes when mice were placed under different behavioral tasks including open-field, high platform, social recognition and T-maze tasks. At the neural network level, the firing frequency of ChCs increased with pyramidal neuron ensemble activity. Optogenetic inhibition of pyramidal neurons lead to diminished activity of ChCs. These results demonstrated a nonselective firing pattern of ChCs, thus preventing the overexcitation of neural network. We conclude that ChCs in the mPFC play an important role in balancing excitation and inhibition of neural networks under natural physiological status.

**Disclosures:** **M. Wu:** None. **J. Xu:** None. **L. Lin:** None. **Y. Gu:** None.

**Poster**

**PSTR049. Inhibitory Control and Disorders of Executive Functions**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR049.05/Web Only

**Topic:** H.04. Executive Functions

**Support:** NRF Grant 2020M3C1B8081319

**Title:** Out-of-phase transcranial alternating current stimulation across anterior cingulate and dorsolateral prefrontal cortices modulates brain activation in inhibitory control

**Authors: *B.-K. MIN**, J. SEO, J. LEE, Y. KIM, J.-C. PARK, J. KWON;
Korea Univ., Seoul, Korea, Republic of

**Abstract:** Transcranial alternating current stimulation (tACS) is useful for improving cognitive abilities non-invasively. One of the essential cognitive abilities is the capacity to effectively regulate task-irrelevant or distracted information processing, referred to as “inhibitory control”. This is predominantly processed in the dorsal anterior cingulate cortex (dACC) and dorsolateral prefrontal cortex (DLPFC), the primary centers of the inhibitory-control network. In this study, a functional magnetic resonance imaging (fMRI) experiment was conducted to investigate if a tACS with a phase lag (0 and 180 degrees) across the dACC and left DLPFC modulated

inhibitory-control performance. Twenty-five healthy participants performed a Stroop task while being scanned using fMRI before and during the phase-lagged tACS treatment. Differences in brain activation were analyzed between the in-phase (0 degree) and out-of-phase (180 degree) conditions. Specifically for the incongruent condition, significantly better performance was observed in the 180°-phase-lag tACS condition compared to the 0°-phase-lag tACS condition, which was also reflected in activation changes in the putamen area. Presumably, the out-of-phase tACS across the dACC and DLPFC assisted in facilitating the inhibitory regulation of incongruent information processing. Taken together, this study exhibited a neuromodulatory feasibility of a phase-lagged tACS on the inhibitory-control function.

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**Poster**

**PSTR049. Inhibitory Control and Disorders of Executive Functions**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR049.06/QQ7

**Topic:** H.04. Executive Functions

**Support:** NIH Grant ZIAMH002955

**Title:** Individualized fMRI-Guided rTMS During a Numerical Stroop Task; Lessons Learned from a Replication Attempt

**Authors: *H. GURA**, Z. REZAEE, E. EKPO, Z.-D. DENG, B. LUBER, S. H. LISANBY, L. BEYNEL;
NIMH, Bethesda, MD

**Abstract:** Online repetitive Transcranial Magnetic Stimulation (rTMS) combines noninvasive brain stimulation with a task to causally study cognitive processes. A 2009 study by Sack et. al. demonstrated a superiority of active rTMS over sham stimulation on a numerical Stroop task (NST), using individualized fMRI targeting. With many technological advancements since 2009, we sought to replicate the rTMS effect on the NST. Our study used updated MRI parameters, a robotic arm to hold the TMS coil, electrical sham stimulation, increased task practice, and a larger sample size. In the NST, two digits varying in physical and numerical size were displayed and subjects had to select the numerically larger digit. Three conditions were tested: Congruent, the numerically larger digit was physically larger; Incongruent, the numerically smaller digit was physically larger; Neutral, both digits were the same size. Nineteen healthy adults (5 male, 39 ± 14 years old) were enrolled. In a first session, subjects practiced and then performed the NST during fMRI acquisition. Individualized TMS targets were defined in the right intraparietal sulcus. In a second session, after practicing, active and sham rTMS was delivered during the NST. Analysis of reaction time (RT) with a repeated measure ANOVA on 14 subjects (four withdrew, one outlier was removed) uncovered a learning effect and a significant interaction

between Stimulation (active/sham), Congruency (incongruent/congruent/neutral), and Stimulation Order (active first/sham first) ($F(2,24) = 4.08$; $p = 0.03$). Lower RTs were found with active rTMS in incongruent trials, but only for participants who received sham rTMS first. Like Sack et al., we stimulated at 60% of the maximum stimulator output; however, the relative intensity varied greatly between subjects, ranging from 94 % to 188% rMT (128 ± 6% on average). Computing rTMS effect as the % change in RT with active compared to sham stimulation, we found a significant correlation ($r = -0.72$, $p = 0.004$), with higher stimulation intensity relative to rMT resulting in a stronger rTMS effect. We could not replicate the difference in RT with active rTMS versus sham. Our training results suggest Sack et al.'s rTMS effect may be a result of learning during experimental blocks. With our larger sample size, we evaluated stimulation order and found a potential cumulative rTMS effect, suggesting that active and sham stimulation should occur on separate days. Further, by determining rMT, we identified stimulation intensity as a confound and suggest individualizing the intensity rather than using a fixed intensity. Our work suggests further improvements are necessary to optimize this experimental paradigm.

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**Poster**

**PSTR049. Inhibitory Control and Disorders of Executive Functions**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR049.07/QQ8

**Topic:** H.04. Executive Functions

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The Thailand Science Research and Innovation (TSRI) Basic Research Fund (fiscal year 2021 under project numbers 64A306000016 and fiscal year 2020 under project number 62W1501) to SI
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The National Research Council of Thailand grant (fiscal year 2021-2023) to SI

**Title:** Real-time feedback amplifies the interactive effect between conflict expectation and stimulus incongruency on a speech-to-text Stroop application

**Authors: K. THANASUAN**[1], P. CHANTAWONG[3], P. PUKAMKOM[3], P. PHUNCHONGHARN[4], *S. ITTHIPURIPAT[2];
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**Abstract:** Feedback is crucial for keeping people engaged in cognitively demanding behavioral tasks. Previous research has demonstrated real-time feedback could enhance behavioral performance in tasks involving working memory. However, the effects of real-time feedback on cognitive control functions, such as conflict monitoring, and its influence across different age groups remain unclear. To address these questions, we developed a web-based speech-Stroop application that provided real-time feedback to users from three age groups: young adults (18-40 years), middle-aged adults (41-60 years), and older adults (61-80 years). The study aimed to investigate how feedback affected conflict expectation and stimulus incongruency in the speech-Stroop task, while manipulating the ratio of congruent and incongruent trials in different blocks. Overall, older adults exhibited slower and less accurate responses compared to the younger groups, indicating a decline in executive function with aging. Additionally, older adults experienced greater cognitive interference from incongruent stimuli. Importantly, real-time feedback resulted in longer response times, suggesting that the feedback made participants more cautious. However, no significant interactions were observed between feedback, task factors, or age groups. Furthermore, feedback did not affect overall accuracy levels. Nevertheless, real-time feedback amplified the interactive effects between conflict expectation and stimulus incongruency on accuracy. In trials without feedback, comparable degrees of cognitive interference were observed across different block types with varying ratios between congruent and incongruent stimuli. Conversely, trials with real-time feedback exhibited significantly increased cognitive interference in blocks where incongruent stimuli were rare and unexpected. Notably, these feedback effects on the interaction between conflict expectation and stimulus incongruency were consistent across all age groups. Together, our study provides valuable insights into the influence of real-time feedback on cognitive control processes. The findings can guide the development of user-friendly and engaging cognitive monitoring and training applications suitable for all age groups.

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**Poster**

**PSTR049. Inhibitory Control and Disorders of Executive Functions**

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**Program #/Poster #:** PSTR049.08/QQ9

**Topic:** H.04. Executive Functions

**Support:** NIH grant MH053851

**Title:** Effects of stress on an orbitostriatal projection activated during a motor impulsivity task

**Authors: *M. GIROTTI**[1], M. BOEHMER[1], K. TUITE[2], D. A. MORILAK[3];
[1]Univ. of Texas Hlth. Sci. San Antonio, San Antonio, TX; [2]The Univ. of Texas Hlth. Sci. Ctr. At S, UT Hlth. San Antonio, San Antonio, TX; [3]Univ. of Texas Hlth. Sci. Ctr. at San Antonio, UT Hlth. Sci. Ctr. San Antonio Dept. of Neurosci., San Antonio, TX

**Abstract:** Motor impulsivity, or the inability to restrain a response despite potentially negative consequences, is a symptom shared by bipolar disorder, ADHD and OCD. Stress is known to exacerbate impulsivity in these psychiatric conditions. In previous work we found that chronic unpredictable stress (CUS) increased premature responding in a rodent test of motor impulsivity. We have also shown orbitofrontal neurons projecting to dorsomedial striatum (OFC to DMS projection) are activated during the test. In this study we address whether CUS alters the activation state of this projection during performance, and whether chemogenetic manipulation of the projection can overcome the response to stress. Motor impulsivity was measured with the 1-choice serial reaction time test (1-CSRTT). Premature responses in this test signal the inability of the subject to "wait" for a signal to receive a reward. Animals are trained to master a task with "wait" time of 5 seconds (intertrial interval, ITI 5), then on a separate day they are tested at a longer ITI (ITI 8 sec), that increases premature responding ("challenge" condition). First, we determined if CUS affected activation of the OFC to DMS projection. Rats were injected with retrograde AAV-EGFP in the DMS, trained in the 1-CSRTT to reach stable performance at ITI 5 and given one session of ITI 8. One group of rats was then subjected to CUS, and one group remained in housing for 2 weeks. Following 3 days of reminder sessions, all rats were divided into 3 groups: a group performed the test at ITI 5, one at ITI 8 and one did not perform the behavior. One hour later perfused brains were collected for immunohistochemical analysis of the OFC using anti-GFP and anti-Fos antibodies. We found that compared to the non-stressed group, CUS rats showed decreased activation of the OFC to DMS projection at ITI 8. We also observed decreased Fos expression in non-DMS projecting OFC neurons. To establish whether reduced activation in the OFC to DMS projection was responsible for the behavioral effect of stress we used a floxed-hM3D-Gq/CRE adenoviral approach to activate the OFC-DMS projection in stressed rats. A control group received floxed-mCherry. Activating OFC-DMS neurons did not reverse the stress effects at ITI 8. In conclusion, we identified an OFC-DMS projection that is activated during a motor impulsivity task. Activation of this projection is dampened in stress rats. However, selectively activating this projection does not rescue the behavioral effects of stress. Since CUS causes a general decrease in OFC activation during challenge, it is likely the behavioral effects of CUS are mediated by an interplay of DMS-projecting and non-DMS projecting OFC neurons.

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**Poster**

**PSTR049. Inhibitory Control and Disorders of Executive Functions**

**Location:** WCC Halls A-C

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**Topic:** H.04. Executive Functions

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**Title:** Neural correlates of inhibitory control during a food go/no go task in adolescents with familial obesity risk

**Authors: *L. CHEN**, G. THAPALIYA, E. JANSEN, K. ROSCH, S. DUCK, S. CARNELL; Johns Hopkins Univ., BALTIMORE, MD

**Abstract:** Maintaining a healthy weight requires exertion of inhibitory control when exposed to food stimuli. Individual differences in food-related inhibitory control may therefore help to explain why some individuals are more likely to develop excess weight than others. Maternal obesity is associated with greater risk of obesity in offspring but underlying neural and behavioral mechanisms are not well-understood. We therefore aimed to investigate the influence of maternal overweight on food-related inhibitory control and underlying neural circuits in adolescent offspring. We hypothesized adolescents with raised familial obesity risk would show reduced food-related inhibitory control and altered activation of inhibitory control circuits. We recruited 71 14-18y olds (33M, 38F), of whom 22 were lean with a lean biological mother (lean low-risk, 'lean-LR'), 19 were lean with a biological mother with obesity/overweight (lean high-risk, 'lean-HR'), and 30 had obesity/overweight ('overweight'). All underwent fMRI scanning during a simple food go/no go task in which 'go' trials used a picture of green broccoli, and 'no go' trials used a picture of either French fries or vanilla ice cream in a red bowl (depending on participant preference). Adolescents underwent the task on two separate days: on one they consumed a 474 ml preload of water pre-scan (0 kcal, fasted condition); on another (counter-balanced) a 474 ml milkshake pre-scan (480 kcal, fed condition). The three groups did not differ on age, sex, race, or behavioral performance indicators. Imaging data revealed 'no go' trials activated posterior-medial-frontal cortex, insula and fusiform gyrus across groups, with patterns of activation in fasted and fed conditions being largely similar. In the fasted state, both the lean-HR and overweight groups engaged anterior cingulate cortex to a greater extent than the lean-LR group. Additionally, the lean-HR group showed increased activation in superior frontal gyrus compared to the lean-LR group. In the fed state, the lean-HR group showed increased activation in caudate, insula, inferior parietal cortex and middle frontal gyrus compared to both the lean-LR and overweight groups. Our results demonstrate activation of inhibitory control circuits as well as regions implicated in food reward during a food go/no task, and suggest raised familial obesity risk among adolescents who are currently lean may impact the neural mechanisms engaged during food-related inhibition, potentially reflecting a heightened reward response paired with greater effort required to inhibit responses to food.

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**Poster**

**PSTR049. Inhibitory Control and Disorders of Executive Functions**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR049.10/QQ11

**Topic:** H.04. Executive Functions

**Support:** NRF-2020R1A2C2007193

**Title:** Reduced P3 responses to smartphone apps following an implicit inhibitory training using a modified Go/No-go task

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**Abstract:** Smartphone overuse is a social problem that deserves attention from society. Particularly concerning is the significant rise in unhealthy smartphone usage, which can detriment individuals' everyday life activities. In fact, excessive and problematic use of smartphone is considered one form of behavioral addiction. According to the dual-process model of addiction, increasing inhibitory control can strengthen control over the problematic use of smartphones. In the current study, we used a modified Go/No-go task as an implicit inhibitory training task and assessed its effects on explicit and implicit evaluation of smartphone apps. A total of96individualsat high-risk of smartphone addictionparticipated in this study and were randomly assigned to the Nogo, Go, or Control group. During training, the Nogo group was manipulated to withhold responses to 90% ofaddictivesmartphone apps (e.g., entertainment)and release responses to 90%of utility apps (e.g., mail); this pairing of app-response was reversed in the Go group. The control group equallyreleased and withhold responses for addictive and utility apps. Before and after the training, participants completed the implicit association task (IAT) with various app words and the craving rating task (CRT) with pictures of apps. These apps included addictive and utility apps used in the Go/No-go training task. Changes in inhibitory control was assessed using the stop signal task(SST).Electroencephalography (EEG) data were recorded throughout the entire procedure using a 64-channel Neuroscan system and CURRY8 software. Event-related potentials (ERPs) to pictures of apps during the CRT were analyzed focusing on P3 responses obtained in the central-posterior area (CPz, Pz) with a time window of 350 to 500 ms after stimulus onset. Preliminary data analysesindicated that the pre-post reduction of the P3 responses to addictive apps was greater in the Nogo group as compared to the control group. The P3 responses to utility apps did not statistically differ between the groups.ERPs during the SST were also analyzed, focusing on N1 responses (Fz, FCz; 80 to 130 ms post stimulus onset). Overall, the Nogo group tended to elicit reduced N1 responses to pictures of apps compared to the control group during the SST.These ERP results suggest that implicit inhibitory training over smartphone apps using a Go/No-go task may have the potential to modulate neural mechanisms related to individuals' responses to smartphone apps and may help mitigate the risk of developing problematic use.

**Disclosures: H. Kim:** None. **H. Kim:** None. **S. Kim:** None.

**Poster**

**PSTR049. Inhibitory Control and Disorders of Executive Functions**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

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**Topic:** H.04. Executive Functions

**Support:** NIH Grant DA031695
NIH Grant MH117836

**Title:** Optogenetic inhibition of the orbitofrontal cortex disrupts inhibitory control and stop-signal performance

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**Abstract:** Historically, the orbitofrontal cortex (OFC) has been implicated in a variety of behaviors ranging from reversal learning and inhibitory control to more complex representations of value and task space. While more modern interpretations of the OFC's involvement suggest a role in outcome evaluation, these cognitive processes often require an organism to inhibit alternative or maladaptive responses or strategies. Single unit recordings from the OFC in rats performing a novel variant of the stop-signal tasks showed that while the OFC seemed minimally involved in the inhibition of an inappropriate response, units in the OFC responded highly to the previous experience of conflict, and this heightened activity correlated with slower movement times of the following trial. In order to investigate the role that the OFC plays in conflict adaptation we expressed halorhodopsin (eNpHR3.0) in neurons in the OFC and tested rats on the stop-signal task. In line with the single unit data, yellow light LED activation of the eNpHR3.0 construct did not alter stop signal performance relative to within session no light control trials. However, examination of trial sequence revealed a significant decrease in accuracy on stop trials that followed go trials (gS trials). gS trials are often the most difficult trial type, as repeated experience with relatively habitual go trials often encourages subjects to perform future trials faster. Interestingly, optogenetic inhibition only disrupted stop signal performance when the yellow LED was active at the start of the trial, and did not alter performance when the yellow LED was active on the previous go trial. This suggests that contrary to the implications of the previously described single unit data that the OFC does play a direct role in inhibitory control processes. Future research is needed to understand how this role in inhibitory control contributes to current theoretical frameworks implicating the OFC in value and task space representations.

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**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR049.12/QQ13

**Topic:** H.04. Executive Functions

**Support:** K23 DA045081

**Title:** The neural substrates of inhibitory control for abstinent smokers - a functional magnetic resonance imaging study

**Authors: *K. Z. SALINAS**[1], K. R. HOUSER[2], C. R. BORDNER[3], A. FENDRICH[2], J. FOULDS[3], A. BELLON[2], Q. X. YANG[1], J. E. MUSCAT[3], S. J. WILSON[4], J. LIAO[3], A. L. HOBKIRK[2];
[1]Neurosci., [2]Psychiatry, [3]Publ. Hlth., Penn State Col. of Med., Hershey, PA; [4]Psychology, The Pennsylvania State Univ., State College, PA

**Abstract: Background:** Long-term cigarette use is associated with inhibitory control dysfunction, which is exacerbated in the context of smoking cues. Long-term nicotine use is associated with altered activity in the default mode (DMN), executive control (ECN), and the salience (SN) functional brain networks. Less is known about their role in inhibitory control and cue salience during nicotine abstinence. The goal of this study was to identify the neural substrates of inhibitory control on cigarette cues for abstinent smokers. **Methods:** Abstinent smokers (N=34) completed a cigarette cue task and a cigarette craving question prior to an fMRI smoking go/no-go (GNG) task that was designed to engage smoking incentive salience and inhibitory control. Participants were presented with smoking and non-smoking pictures bordered in blue or yellow and were instructed to press a button box or inhibit their response depending on the border color. Whole brain voxel-wise analyses contrasted inhibition-related brain activation between task blocks with pictures bordered by go and no-go colors vs. only go colors and cue-related activation between task blocks with pictures of smoking and non-smoking stimuli vs. only non-smoking stimuli. Whole-brain voxel-wise correlation analyses determined if brain activation was related to GNG task accuracy and cigarette craving scores. **Results:** There were statistically significant regional inhibition-related activation increases in twelve brain clusters encompassing SN, ECN, and DMN regions. However, there were no statistically significant smoking cue-related regional brain changes. Increased accuracy on the GNG task was related to increased inhibitory activation in the SN and occipital lobe but decreased inhibitory activation in the primary motor and somatosensory motor cortices. Increased craving scores were related to decreased inhibitory activation in the left orbitofrontal cortex and right thalamus/caudate. Increased craving scores were associated with increased cue-related activation of the posterior cingulate cortex and precuneus (i.e., DMN) as well as the occipital lobe, ventral tegmental area, and cerebellum. **Conclusion:** Overall, these results confirm that the DMN, SN, and ECN are important neural substrates for engaging in inhibitory control in the context of smoking cues. SN activation during abstinence may be involved in cognitive performance. Although DMN activation was not associated with inhibition accuracy, there was evidence of aberrant DMN activation during inhibitory control. Additionally, DMN activation in response to smoking cues may contribute to craving during abstinence.

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None. **J. Liao:** None. **A.L. Hobkirk:** 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.; K23 DA045081.

**Poster**

**PSTR049. Inhibitory Control and Disorders of Executive Functions**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR049.13/QQ14

**Topic:** H.04. Executive Functions

**Support:** Phyllis M. Taylor Center for Social Innovation and Design Thinking

**Title:** Music training is related to late ERP modulation and enhanced performance during the Simon but not the Stroop task

**Authors: *M. VELASQUEZ**[1], J. WINSTON[4], S. SUR[5], K. A. YURGIL[6], A. UPMAN[4], S. WROBLEWSKI[2], A. HUDDLE[3], P. J. COLOMBO[2,3];
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**Abstract:** There is increasing evidence that music training is positively correlated with performance on tasks used to measure components of executive function. The Stroop and Simon tasks both measure responses to congruent and incongruent information reflecting cognitive conflict resolution. However, there are many more reports of a music-training advantage in the Simon than in the Stroop task. The Stroop task may engage conflict resolution earlier, at a sensory stage, while the Simon task may do so at a later motor output planning stage. We hypothesize that music experience selectively improves conflict resolution at the late motor output stage. To test this, behavioral responses and event-related potentials (ERP) were measured in people with varying musical experience while they performed the Stroop and Simon tasks. In specific, we hypothesized that musical experience is positively correlated with performance in the Simon but not the Stroop task, and that this relationship is reflected in ERP components in the later stage of motor output processing in the Simon task. All participants (N=22) completed the Goldsmith Musical Sophistication Index and were split at the median into high and low music training groups. Electrical brain activity was recorded while they completed visual Stroop and Simon tasks. Formal music instrument training was negatively correlated with behavioral measures of the Simon effect but not the Stroop effect which is consistent with previous reports. Mean amplitude difference (incongruent - congruent) was greater for the high-music training group than the low-music training group at N100 for sites Cz and Pz in the Simon task and Cz and Fz in the Stroop task, and at N450 at Cz and Pz in the Simon task. N450 difference peaks occurred earlier in the high-music training group than the low-music training group at Pz. Overall, the differences between the high and low music training groups at N100 indicate that

music training may be related to better sensory discrimination. These differences, however, were not related to better behavioral measures of conflict resolution. Differences in N450 responses between groups with high and low levels of music training, particularly in regions encompassing the motor and parietal cortices, suggest a potential role of music training in aiding action selection during response conflict situations. These results are consistent with our hypothesis that music training selectively enhances cognitive conflict resolution during late motor output planning stages.

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**Poster**

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**Topic:** H.04. Executive Functions

**Support:** Phyllis M. Taylor Center for Social Innovation and Design Thinking
Flowerree Fund

**Title:** Effects of acute and long-term mindfulness on the conflict resolution component of attention

**Authors: *D. ELCIN**[1], M. A. VELASQUEZ[1], P. J. COLOMBO[1,2];
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**Abstract:** Experience with mindfulness practices has been associated with improved attentional abilities, especially in the domain of conflict resolution. Previous reports have focused on the effects of extensive mindfulness experience, or the effects of weeks-long mindfulness interventions on novices. To our knowledge, no study has examined the effects of a single mindfulness intervention on conflict resolution in long-term meditators and non-meditators. To address this gap, 20 long-term meditators and 20 non-meditators were recruited and assigned to either a mindfulness condition or a control condition. Each group completed a Stroop Word-Color Task (SWCT) to assess conflict resolution, before and after a mindfulness or a control intervention, while undergoing neural imaging with functional near-infrared spectroscopy. Performance on the Stroop task, and neural activation patterns, were measured among long-term meditators and non-meditators at baseline to determine the effect of long-term mindfulness practice. The pre-post changes in performance on the Stroop task and neural activation patterns were compared between mindfulness and control groups to determine the acute effect of the mindfulness intervention. No significant differences in performance were found between non-meditators and meditators at baseline in the SWCT, indicating that long-term meditation experience does not impact conflict resolution ability. We found no main effect of intervention or expertise on conflict resolution performance in the repeated measures ANOVA, however, only

meditators assigned to the mindfulness condition exhibited improvement in pre-post comparisons. At baseline, meditators displayed greater right-lateralized activation in the prefrontal cortex during conflict resolution compared to non-meditators. Of interest, only the non-meditators who engaged in meditation showed a significant increase in neural activation from pre to post. Specifically, there was an increase in neural activation in the right dorsolateral prefrontal cortex. Overall, these findings suggest that long-term meditation experience may alter the lateralization of attention networks involved in conflict resolution. Engaging in mindfulness before conflict resolution may be beneficial for individuals already experienced in mindfulness. For those with no experience, mindfulness may tax cognitive resources and impair conflict resolution performance immediately afterward.

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**Poster**

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**Topic:** H.04. Executive Functions

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**Title:** Interplay between the noradrenergic and cholinergic system modulates inhibitory control

**Authors: *Y. LIU**[1], C. MARTINEZ[1], J. FENG[2], G. LI[2], Y. LI[2], Q. WANG[1];
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**Abstract:** Inhibitory control is an essential executive function for goal-directed behavior. It allows individuals to resist inappropriate behaviors and enhance self-regulations in order to maximize future rewards. Previous work suggests that multiple neuromodulatory systems throughout the entire brain play a role in regulating inhibitory control. However, the extent to which the noradrenergic and cholinergic systems, as well as their interplay, modulate inhibitory control remains poorly understood. Using genetically encoded norepinephrine (NE) and acetylcholine (ACh) fluorescent biosensors, we simultaneously measured the NE and ACh dynamics in the brain of mice performing an inhibition control task. In this behavior paradigm, water-deprived animals were trained to withhold their habitual licking of the water spout for a variable period cued by a tone. Premature licking resulted in a brief punishing air puff to the face, while successful withholding was rewarded with sweet water. Our data revealed a strong coherence between NE and ACh dynamics at the frequency of 0.3 to 0.8 Hz, with dynamic phase relationships (i.e. synchronous coupling and oscillatory states). Our data further indicated a significant correlation between behavioral outcomes and the interaction of the NE and ACh

systems, specifically with increased switching from coupled to oscillatory states in failed trials compared to successful trials. We hypothesize that this correlation is modulated by the locus coeruleus (LC)-basal forebrain (BF) circuitry. To validate our hypothesis, we expressed retrograde DREADDs in different transgenic mouse lines and selectively inhibited the BF-projecting LC neurons or LC-projecting BF neurons through CNO treatment. Our data showed that following the inhibition of BF-projecting LC neurons, animals achieved a lower performance of withholding their licks and waited longer time before collecting the water reward, together with a decreased correlation between behavioral outcomes and the NE-ACh interaction compared to the control or possible LC-projecting BF neurons manipulation group. Taken together, our findings provided insights into the functional significance of the interplay between the noradrenergic and cholinergic systems and suggested the relevance of the LC-BF circuitry in modulating inhibitory control processes.

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**Poster**

**PSTR049. Inhibitory Control and Disorders of Executive Functions**

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**Topic:** H.04. Executive Functions

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**Title:** Motor decision is influenced by the difficulty of solving a numerical comparison in a selective stop signal task

**Authors:** I. MARC[1,2], M. SEGRETI[1], V. GIUFFRIDA[1,2], S. RAMAWAT[1], A. PAUL[1,2], G. BARDELLA[1], P. PIERPAOLO[1], S. FERRAINA[1], ***E. BRUNAMONTI**[1];
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**Abstract:** The environment's variability often requires us to assess whether an ongoing action should be completed or promptly interrupted in the event of an unforeseen circumstance. In experimental settings, these environmental interactions are simulated through selective versions of the Stop Signal Task (selective SST). These tasks require evaluating whether to cancel or not a planned movement based on the information provided by signals discriminated for the different perceptual characteristics. A theoretical model has been developed to explain the task's outcomes, wherein a Go and a Stop process engage in a race towards a common finish line. Within this framework, interpreting an event occurring during motor preparation as a countermanding input has been found to influence the race's dynamics. However, sometimes, deciding whether to ignore a stop signal requires going beyond simple perceptual processing and

evaluating its impact on the ongoing decision. In our study, we investigated how the difficulty in the engaged cognitive operation for interpreting an external stimulus as a command to countermand ongoing action influences action inhibition. To do so, we designed a stimulus-selective version of the SST, where 18 participants were required to engage in a selective finger movement or inhibition, based on a numerical comparison. They were instructed to make a comparison between two numbers presented in the opposite positions of the screen and lift the index finger if the number on the left side of the screen was higher or lift the middle finger for the opposite arrangement of the numbers. After a variable delay, randomly chosen between two possible values, in 40% of trials the higher number on the screen was replaced by a smaller number (Stop signal) or by a larger number (Ignore signal) than the target one. By manipulating the numerical distance between the numbers to be compared, whereas reaction time was longer when comparing close numbers such as 5 vs. 6 than distant numbers such as 5 vs. 9. This subsequently influenced both the probability of correctly stopping a programmed movement and the corresponding reaction time to the stop signal (SSRT). Specifically, we found a significantly lower proportion of correctly inhibited movements for shorter numerical distances compared to longer ones (two-way ANOVA, ps < .05), and a gradual decrease in SSRT with increasing numerical distance (one-way ANOVA, p < .05). Overall, our results suggest that cognitive operations need to be considered in understanding how action inhibition occurs in complex contexts.

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**Poster**

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**Topic:** H.04. Executive Functions

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**Title:** Individuals with Low Sensitivity to Alcohol Exhibit Dysregulated Inhibitory Control Task Performance and Neural Circuit Function: A Pilot fMRI Study

**Authors:** *S. UPTON[1], **R. U. COFRESI**[1], M. RODGERS[1], A. A. BROWN[1], R. EBADA[1], T. M. PIASECKI[2], B. D. BARTHOLOW[1], B. FROELIGER[1];
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**Abstract: Background**: Low sensitivity (LS) to the acute pharmacological effects of alcohol confers risk for alcohol use disorder (AUD). Although alcohol-related cues can impel alcohol approach behavior among individuals with LS, the ability of LS individuals to exert inhibitory control (IC) over behavioral impulses remains under-explored. In this study, we used an event-related fMRI IC task to explore IC and its neural mechanisms among LS ($n$ = 16; 56% female) and high sensitivity (HS; $n$ = 17; 59% female) individuals aged 18-23 yrs ($M$=20.42; $SD$=1.25). **Methods**: The LS and HS groups were determined based on scores on the Alcohol Sensitivity Questionnaire (ASQ). IC was assessed using a Go-Go / NoGo (GGNG) task - a well-validated task probe of the hyperdirect pathway, including the right inferior frontal gyrus (rIFG), and right supplementary motor area (rSMA). Task performance (% correct omissions on NoGo trials) along with blood oxygenation level-dependence (BOLD) response within these regions and effective connectivity (EC) between regions were analyzed. **Results**: Controlling for individual differences in alcohol use quantity-frequency across the past year, the following was observed: (i) a non-significant group difference (LS < HS) in NoGo trial accuracy: $M_D \pm SE_D$= -9.54 ± 5.81, $T$(30)=-1.64, $p$=.111; (ii) a significant group difference (LS < HS) in the magnitude of BOLD response during correct NoGo trials in the rIFG and rSMA: $M_D \pm SE_D$= -1.24 ± 0.60, $T$(30)=-2.05, $p$=.049; $M_D \pm SE_D$= -1.28 ± 0.38, $T$(30)=-2.05, $p$=.002; and (iii) collapsing across groups, a marginally significant medium-size positive association of NoGo accuracy with EC from the rIFG to the rSMA: $r$(30)=+.31, $p$=.088. **Conclusions**: These findings suggest that disrupted hyperdirect pathway function during IC may contribute to an LS endophenotype. Such IC deficiencies may give rise to LS individuals' difficulty stopping once a drinking episode has been initiated. However, further research is needed to examine whether: (a) hyperdirect pathway EC mediates IC and drinking behavior; (b) strategies for potentially treating dysregulated IC (e.g., repetitive transcranial magnetic stimulation); and (c) whether LS individuals are more amenable, relative to HS individuals, to novel approaches for treating dysregulated IC.

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**Poster**

**PSTR049. Inhibitory Control and Disorders of Executive Functions**

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**Program #/Poster #:** PSTR049.18/QQ20

**Topic:** H.04. Executive Functions

**Title:** Assessing cognitive flexibility in rhesus macaques and humans with a novel multidimensional set-shifting task

**Authors: *P. YURT**[1,3,5], A. CALAPAI[1,5], R. MUNDRY[5,2,4], S. TREUE[1,5];
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**Abstract:** Cognitive flexibility (CF) is an executive function helping individuals to adjust their behavior based on changes in the environment and internal needs. Paradigms for determining set shifting (shifting between rules) and reversal learning (reversing the current rule to swap the reward contingencies of options) are successful in measuring CF in a variety of species. But the transferability of the data is low, due to differences in how these tasks are adapted to each species. Here we assess CF for both rhesus macaques and humans without species-specific task modifications.We developed a novel computerized paradigm, combining elements of set shifting (intradimensional (ID) and extradimensional (ED) shifts) and reversal learning (discrimination and reversal stages) tasks. Four stimuli, target, distractor and 2 neutrals, appear on a touchscreen. Each stimulus combines a shape, color and motion direction, the latter used in a set shifting paradigm for the first time. In each cycle (discrimination-reversal pair) one of the features is relevant and subjects find the target by trial and error. A trial ends when a target or distractor is touched. With neutrals, we allow for a foraging approach as they disappear upon touch without terminating the trial.We assessed cognitive flexibility of 11 rhesus macaques and 25 adult humans with our task, which required little to no training (1 day for humans and an average of 6 days for monkeys). In the monkeys we observed a strong selection bias for the stimulus located towards the bottom of the screen. To identify whether this bias has been induced by the structure of our task, we assessed, with 4 animals, a configuration of stimuli where each stimulus is equally distanced from the start button. Animals still show a preference for certain locations, different for each, suggesting that what might be considered a location could instead be a strategy for reducing the number of options and therefore the corresponding cognitive load of each trial. CF was consistent across different feature dimensions in both species, suggesting that the same mechanism is responsible for dealing with a rule change, regardless of the feature dimension of the sensory input. Thus, visual motion is a suitable feature dimension for CF tasks. We observed that humans perform better during ID compared to ED shifts, shifting between rules within the same and different feature dimension, respectively. As we do not see such a difference for the monkeys, the two species might be using different strategies to solve the task, with humans showing a level of flexibility that is categorically different from that of rhesus monkeys.

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**Topic:** H.04. Executive Functions

**Support:** University of Michigan, college of LSA

**Title:** Causal evidence for the role of lateral prefrontal cortex in the time course of interference resolution

**Authors: *J. SELLERS**, T. J. ADKINS, H. ZHANG, J. JONIDES, T. G. LEE;
Univ. of Michigan, Ann Arbor, MI

**Abstract:** We often find ourselves in situations in which well-learned and nearly automatic responses conflict with our goals. Imagine making a right turn while driving in the United Kingdom after years of driving in the United States. You would likely have an automatic tendency to turn into the near lane and cognitive control is required to make the goal-directed response of turning into the far lane instead. This process of interference resolution is typically studied using conflict tasks such as the Simon task. Studies using fMRI and non-invasive brain stimulation that have examined conflict tasks have repeatedly implicated the right dorsolateral prefrontal cortex (DLPFC) in the interference-resolution process. However, it is unclear from these data whether this brain region is responsible for inhibiting prepotent responses, enhancing goal-directed processing, or some combination of both. We argue that the reason is twofold. First, the typical approach of using free RT to index interference resolution using RT difference scores cannot reveal the temporal dynamics of prepotent and goal-directed processing. Second, computational models capable of quantifying the underlying processes associated with prepotent and goal-directed processing are only weakly informed by data obtained using free RT. We believe a way forward in understanding the role of DLPFC in cognitive control is by specifically investigating the time course of interference resolution using a new task paradigm called the "forced-response method". Participants performed a version of a Simon task in which they were forced to respond at a predetermined time. In the forced-response paradigm, stimulus onset is varied and participants are trained to respond at a specific time, transforming the time available for response preparation into an independent variable controlled by the researcher. This method lends itself well to a probabilistic model of response preparation that is able to tease apart the preparation of prepotent and goal-directed responses by estimating the latency of the cognitive processing required for each response. Just prior to task performance, we used a transcranial magnetic stimulation (TMS) protocol, continuous theta-burst stimulation (cTBS), to transiently disrupt activity in right DLPFC to investigate its causal role in interference resolution. Preliminary evidence suggests that, relative to stimulation over a control site, DLPFC disruption disinhibits the preparation of prepotent responses and has a minimal impact on the latency of goal-directed responses. These results provide strong causal evidence for the precise role of right DLPFC in interference resolution.

**Disclosures: J. Sellers:** None. **T.J. Adkins:** None. **H. Zhang:** None. **J. Jonides:** None. **T.G. Lee:** None.

**Poster**

**PSTR049. Inhibitory Control and Disorders of Executive Functions**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR049.20/QQ22

**Topic:** H.04. Executive Functions

**Support:** R01MH057414
R01MH117785

**Title:** Amygdala and hippocampal innervation of projection neurons and interneurons in the nucleus accumbens shell of rhesus monkeys

**Authors: *L. MARSHALL**, H. BARBAS;
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**Abstract:** The Nucleus Accumbens (NAc) is critical for motivated behavior and its dysfunction is associated with several psychiatric disorders, such as substance use disorder and depression. The shell of the NAc is innervated by both the hippocampus and amygdala, thus positioning it as a key interface between the limbic and motor systems. There are primate-specific specializations in the NAc shell circuitry that challenge the translation of scientific advances from rodent models to humans. One difference pertains to the significant increase in interneuron populations in primates. To address this issue in the rhesus macaque, we first conducted a detailed stereological analysis of the population of the projection neurons, which were labeled with DARPP-32, and two non-overlapping populations of interneurons, labeled with calretinin (CR) or parvalbumin (PV). We found that from the combined population of neurons, approximately 76% were DARPP-32+ projection neurons, 16% were CR+ interneurons, and 8% were PV+ interneurons. These estimates do not include the sparse cholinergic interneurons. These findings show a significant shift in primate NAc interneuron populations compared to rodent estimates of 5-10%, and in which PV+ interneurons are the dominant subtype. We then studied innervation patterns by tracer-labeled pathways from the amygdala and the hippocampus onto three types of striatal neurons which were fluorescently tagged for CR, PV, or DARPP-32. Appositional analysis with confocal microscopy revealed that both pathways disproportionately innervated intrinsic interneurons over projection neurons based on their respective populations. Additionally, the pathway from the amygdala apposed CR+ interneurons three times more frequently than the PV+ interneurons. The shift in neuron populations and increased innervation of the intrinsic circuitry by limbic pathways suggest specializations in primates that underscore the complex functions attributed to the NAc shell for motivated behavior and disruption in psychiatric diseases.

**Disclosures: L. Marshall:** None. **H. Barbas:** None.

**Poster**

**PSTR049. Inhibitory Control and Disorders of Executive Functions**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR049.21/QQ23

**Topic:** H.04. Executive Functions

**Support:** NIMH R01-MH118500

**Title:** Biophysical Neural Model of Core and Matrix Thalamocortical Systems in Rodents and Primates

**Authors: *N. MATUK**, A. YAZDANBAKHSH, B. ZIKOPOULOS;
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**Abstract:** The thalamocortical (TC) circuit has a key role in cognitive sensory-motor processing, memory, emotion, and sleep spindle generation during wakeful and sleep states. Topographically- and functionally-organized interactions between the cortex, thalamus, and inhibitory thalamic reticular nucleus (TRN) underlie these diverse functions, including specialized reciprocal communication between the TRN and thalamic neurons through open or closed loop connections. The circuit is further subdivided into two functionally and anatomically distinct circuits: the core and matrix. Core circuits are more involved with sensory processing, while matrix circuits are more involved with limbic processing. While rodents and primates both have similarly organized thalamocortical circuits, they critically differ in the presence of local thalamic interneurons (IN); rodents have a very limited thalamic IN population in contrast to the extensive population of thalamic INs found in primates. We developed a rodent and primate biophysical neural model of the core and matrix thalamocortical circuits, based on recent physiological and anatomical data. Our model allowed us to investigate patterns of synchrony and spindling through spatiotemporal maps and band-passed neural signal averages. Our primate model was able to generate synchrony faster than the rodent model regardless of the arrangement of the TRN-thalamus interactions. With regards to spindle patterns, our primate matrix spindles had higher amplitudes than rodent matrix spindles and the open-loop primate spindles had an overall higher spindle density than open-loop rodent spindles. Our model provides a platform for understanding how the differences in the rodent and primate TC circuits can lead to network and spindle pattern differences that could have functional implications with memory consolidation.

**Disclosures:** **N. Matuk:** None. **A. Yazdanbakhsh:** None. **B. Zikopoulos:** None.

**Poster**

**PSTR049. Inhibitory Control and Disorders of Executive Functions**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR049.22/QQ24

**Topic:** H.04. Executive Functions

**Support:** NIH Grant R01MH117785
NIH Grant R01MH057414

**Title:** Inhibitory neuronal subpopulations in the entorhinal and perirhinal cortices in rhesus monkeys

**Authors: *J. BAUTISTA**[1], V. VERMA[2], H. BARBAS[3];
[2]Hlth. Sci., [3]Helen Barbas, [1]Boston Univ., Boston, MA

**Abstract:** The hippocampus (HPC), entorhinal (EC or A28), and perirhinal (PRC) (composed by A35 and A36) cortices in the medial temporal lobe (MTL) contribute to multiple aspects of memory processing. The EC and PRC receive cortical input from multimodal association areas

and the amygdala. The EC primarily receives feedforward projections from the PRC that terminate largely in layers I-III and sparsely in layer V, while the EC sends feedback projections to PRC. The PRC projects to EC, which then projects to the dentate gyrus of HPC, shaping the EC as the gateway to hippocampus. The complex processing in EC and PRC is fine-tuned by functionally and neurochemically distinct types of inhibitory neurons labeled for calretinin (CR), parvalbumin (PV), and calbindin (CB), which account for most of the inhibitory neuronal population in the primate cortex. Here we characterized the inhibitory populations in each layer of the EC and PRC of the rhesus macaque. We used stereological methods to estimate the density of CR, PV, and CB neurons in the rostral regions of the EC and PRC. Our results showed that in EC and PRC, CR neurons had the highest density followed by CB, while PV neurons had the lowest density. Agranular A35 had an overall lower density of all neurochemical classes of inhibitory neurons in comparison to dysgranular A36. The medial subdivisions of the rostral EC had a higher density of CR neurons in the deep layers, particularly in layer Va. In contrast, the density of PV neurons was higher in the deep layers of the lateral subdivisions of the rostral EC, especially in layer Va. Since the EC receives the output from the HPC via layer Vb and is thought to send projections to other cortical areas and PRC via layer Va, the inhibitory profile of these sublayers can shed light on the potential impact of inhibitory neurons in these circuits. The EC and PRC are affected in neurodegenerative disorders such as Alzheimer's disease, with atrophy and neuronal loss in the ventral temporal cortex. These findings provide the basis for future comparison with information from neurotypical human brains and in neurodegenerative diseases.

**Disclosures:** **J. Bautista:** None. **V. Verma:** None. **H. Barbas:** None.

**Poster**

**PSTR049. Inhibitory Control and Disorders of Executive Functions**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR049.23/QQ25

**Topic:** H.04. Executive Functions

**Support:** R01NS120987
R01MH116043

**Title:** Sex differences in dopamine dynamics during amphetamine withdrawal in mice.

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[2]Univ. of Iowa, [1]Univ. of Iowa, Iowa City, IA; [3]Univ. of Iowa Roy J and Lucille A Carver Col. of Med., Univ. of Iowa Roy J and Lucille A Carver Col. of Med., Iowa City, IA

**Abstract:** Amphetamine and other substance use disorders (SUD) are characterized by a diverse population of patients and no pharmacological treatment options. Effectively treating everyone suffering from SUD requires a better understanding of the neural mechanisms that underlie the

differences between SUD populations like the large sex differences that exist. For example, females transition from initial use to dependance quicker, and report more adverse withdrawal symptoms. Cognitive impairments contribute to the maintenance of SUD. However, the sex differences in the SUD-related cognitive impairments or mechanisms behind these impairments are unknown. Dorsal striatal dopamine is implicated in both optimal cognitive performance and the sex differences found in SUD. To understand the sex differences in SUD-related cognitive impairments, we trained mice on an interval timing task, which requires cognitive processes such as working memory and attention. We recorded their performance throughout amphetamine withdrawal. Once trained, mice were exposed to chronic amphetamine (2.5 mg/kg i.p. daily) for 14 days followed by a forced withdrawal period of 14 days during which they performed the interval timing task daily. My preliminary data suggests that during withdrawal, females in the diestrus stage of their reproductive cycle displayed anticipatory responding, i.e., these mice responded earlier compared to baseline. Interestingly, both females in the estrus stage of the cycle and males did not display differences compared to baseline performance. This suggests an estrus-dependent change in their interval timing during amphetamine withdrawal. To determine if dorsal striatal dopamine dynamics contribute to this behavioral difference, we will use dLight, a florescent dopamine indicator to observe sub-second changes in relative dopamine dynamics during the interval timing task. Understanding dorsal striatal dopamine dynamics during amphetamine withdrawal will inform sex-specific mechanisms of cognitive dysfunction in SUD, and will inform novel treatment options for SUD.

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**Poster**

**PSTR049. Inhibitory Control and Disorders of Executive Functions**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR049.24/QQ26

**Topic:** H.12. Aging and Development

**Support:** NIMH Grant R01MH126531

**Title:** Observer-based assessment of neurodevelopment in two-year-old toddlers born to mothers with and without documented SARS-CoV-2 infection during pregnancy

**Authors: *I. AHMED**[1], A. LAVALLEE[1], M. KYLE[1], M. FIRESTEIN[2], M. HUSSAIN[1], L. SHUFFREY[2], Y. HU[1], C. RODRIGUEZ[1], K. FISHER[1], G. KURMAN[1], V. CHAVES[1], S. HODSON[1], R. FISCHMAN[1], D. DUMITRIU[1];
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**Abstract: Background.** While instances of vertical transmission following prenatal exposure to SARS-CoV-2 are rare, it is important to consider alternative mechanisms through which child neurodevelopmental changes can occur. Maternal immune activation, for instance, can act as a

‘neurodevelopmental disease primer,’ potentially influencing child neurodevelopment. Previous data on infants exposed to maternal SARS-CoV-2 infection prenatally, using both parent-reported and observational measures, did not suggest an association with adverse neurodevelopmental outcomes at 5-11 months of age. Here, we investigated whether similar non-significant associations are observed at 24-32 months of age, in a subset of mother-infant dyads enrolled into the COVID-19 Mother Baby Outcomes (COMBO) Initiative. **Methods.** A subset of mother-infant dyads with documented (exposed) SARS-CoV-2 infections and matched unexposed dyads enrolled into the COMBO Initiative were included here. Toddler neurodevelopment was assessed using the telehealth adapted Developmental Assessment of Young Children, 2nd edition (DAYC-2), which was conducted over Zoom when the toddlers were between 24- and 32-months old. The primary outcome of interest was age-adjusted standard scores on five DAYC-2 subdomains: cognitive, gross motor, fine motor, expressive language, and receptive language. The association between DAYC-2 age-adjusted standard scores and SARS-CoV-2 exposure was assessed using adjusted linear regression models. Data were analyzed from 169 toddlers. **Results.** When adjusting for sociodemographic variables, our analysis revealed no significant association of SARS-CoV-2 exposure with child neurodevelopment on any of the five subdomains of the DAYC-2. **Conclusions.** Preliminary results did not suggest an association between SARS-CoV-2 in utero exposure and toddler DAYC-2 scores on any subdomains at 24-32 months. Additionally, the longitudinal stability of age-adjusted subdomain scores will be examined by analyzing data from 65 dyads who completed both the 5-11 month and 24-32 month DAYC-2 assessments.

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**Poster**

**PSTR050. Animal Behavior and Social Cognition I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR050.01/QQ27

**Topic:** H.06. Social Cognition

**Support:** NSERC

**Title:** Social recognition memory is rapidly mediated by an interaction between estrogens and oxytocin in female but not male mice

**Authors: *P. PALETTA**, *P. PALETTA, A. PALMATEER, G. DHUGA, E. WATSON, E. CHOLERIS;
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**Abstract:** Social recognition (SR) is the ability to distinguish between conspecifics based on previously acquired information. Research has shown that both estrogens and oxytocin (OT) play

significant roles and are needed for SR. For example, gene knockout of estrogen receptors (ERs), OT, or OT receptor (OTR) each impairs SR. From this research it was proposed that estrogens and OT may interact to affect SR. A model of this interaction was hypothesized (Choleris et al., 2003, PNAS) where estrogens binding to the ERs expressed in the paraventricular and supraoptic nuclei (PVN and SON) of the hypothalamus, where the majority of OT is produced in the brain, to facilitate the production/release of OT. The OT will then bind to the OTR in the medial amygdala (MeA), which also receives projections from the olfactory bulbs. The OT/OTR binding allows the incoming olfactory information to be used to recognize a familiar conspecific. This research tested whether this interaction occurs as described above and if it occurs through estrogens rapid mechanisms. In these experiments SR was tested using a rapid "difficult" SR paradigm. This paradigm has 2 sample phases, in which 2 stimulus mice are presented to the experimental mouse for 5 minutes. This is followed by a 5-minute test phase where 2 stimulus mice are presented again, however one is a novel mouse. Since mice prefer novelty, if the novel mouse is investigated more than the previously met mouse, it indicates SR. In the first experiment, we found that 17b-estradiol (E2) infused into the PVN rapidly facilitated SR (at doses of 25 and 50nM) in female but not male mice, and this facilitation was blocked by the infusion of an OTR antagonist (OTRA) into the MeA at a subeffective dose (75nM) that by itself dose not block SR. Next, we investigated which ERs in the PVN mediate this interaction by infusing agonists for ERb (DPN) or GPER (G1) into the PVN. We found that both DPN (at 100 and 150nM) and G1 (at 100 and 200nM) rapidly facilitated SR and the facilitation caused by each was blocked by infusing the same OTRA does to the MeA. Lastly, we demonstrated that this interaction also occurs in the SON. Infusions of E2 (at 25 and 50nM) rapidly facilitated SR and this facilitation was also blocked by MeA infusion of the subeffective OTRA dose. Taken together these results indicate that E2 in both the PVN and SON of female mice mediates SR by interacting with the OTR in the MeA and the facilitation of SR that occurs in the PVN is mediated by both ERb and GPER. These results also support the proposed idea that estrogens and OT interact to rapidly mediate SR in female mice and that this interaction occurs in the way the model described.

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**Poster**

**PSTR050. Animal Behavior and Social Cognition I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR050.02/QQ28

**Topic:** H.06. Social Cognition

**Support:** JSPS KAKENHI JP 16K01959
JSPS KAKENHI 21H05813

**Title:** Category information in the inferior temporal and prefrontal cortex during the symbolic categorization of animate and inanimate objects in natural movies

**Authors: *R. ICHWANSYAH**[1,2], K. ONDA[1,2], J. EGAWA[2], A. SUGIMOTO[3], T. MATSUO[4], T. SUZUKI[5], T. SOMEYA[2], I. HASEGAWA[1], K. KAWASAKI[1];
[1]Dept. of Neurophysiol., [2]Dept. of Psychiatry, [3]Dept. of Community Psychiatric Med., Niigata Univ., Niigata, Japan; [4]Tokyo Metropolitan Neurolog. Hosp., Tokyo, Japan; [5]Natl. Inst. of Information and Communications Technol., Osaka, Japan

**Abstract:** Conceptual categorization is a fundamental cognitive ability underlying human intelligence, such as thinking and reasoning. Behavioral studies have shown that monkeys are able to categorize food/non-food and animate/inanimate objects with respect to biologically important objects. However, past studies have had issues that the indices are indirect or the experimental environment is uncontrolled. In the present experiment, we tested category representations in the prefrontal cortex (PFC) and inferior temporal lobe (ITC) using an experimental design in which categories were explicitly discriminated using symbols and natural movie stimuli.Two monkeys (M. fuscata) were trained to perform an animate/inanimate symbolic category task. Subjects were trained to select the "animate symbol" when presented with a 2-second movie clip depicting a moving animal, and to select the "non-animate symbol" for a moving non-living object under free gaze. Electrocorticography was conducted from the ITC (128 channels) and PFC (64 channels). Averaged event-related potentials showed mainly transient responses immediately after the onset of stimulus presentation, and sustained responses were not evident. Event-related spectral perturbation revealed a sustained response in the high-frequency (γ) band in response to animated stimuli. Population decoding analysis of the ITC and PFC showed that their accuracy was highest immediately after the start of the movie, but that both areas maintained high accuracy for 2 sec until the end of the movie. γ-band signals, in particular, showed significantly higher accuracy during the sustained period. Decoding was also performed using independent components to identify the spatial distribution of categorical information. The results showed that the most informative components were localized in the superior temporal sulcus (STS) for ITC and in the dorsomedial region for PFC (dmPFC). We also conducted a stepwise searchlight decoding to verify the importance of spatial patterns of activity. Compared to single-channel decoding, multiple-channels searchlight decoding improved performance, suggesting the importance of spatial activity patterns. In addition, spatial activity patterns, including STS channels, performed better in the ITC, while patterns including dmPFCs performed better in the PFC. These results suggest that frequency-specific spatial activity patterns of the STS and its surrounding areas and dmPFC and its surrounding areas, are sustained during gaze following objects in the natural moves, thereby maintaining the category representation of animate and inanimate objects and forming links to symbols.

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**Poster**

**PSTR050. Animal Behavior and Social Cognition I**

**Location:** WCC Halls A-C

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**Topic:** H.06. Social Cognition

**Support:** NRF-2022R1A2C3008991
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NRF-2019M3E5D2A01058328

**Title:** Individual variance for minimizing competition in a multi-agent system

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[1]Dept. of Brain and Cognitive Sci., [2]Life Sci. Res. Inst., Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of

**Abstract:** In multi-agent systems, interactions among agents pose critical challenges during efforts to optimize the system (Rossi 2018). In particular, the pursuit of individual goals can have detrimental effects on the entire system, as agents with similar behaviors may come into competition. This problem can be often observed in certain scenarios such as traffic jams, which occur when all agents choose the same shortest route that is observed to be ideal in the single-agent condition (Sugiyama 2008). Previous studies in the area of deep reinforcement learning have suggested that this problem can be handled by considering other agents' behaviors as part of the environment (Nguyen 2019), but this approach has limited applicability in high-dimensional scenarios due to the increased computational cost. Here, we show that clues can be found from the classical fuzzy theory (Klir 1995), in which uncertainty during the decision-making process can be utilized to achieve the optimization of a complex system. Similarly, we demonstrate that randomness in individual behaviors can be utilized as a multi-agent optimization strategy. We simulate a multi-agent road traffic model in which agents navigate a grid-shaped road towards their destinations. The average speed of each road is periodically updated, and agents are provided with the shortest path information. We found that when all agents strictly follow the "ideal" path, congestion occurs and the average time cost increases dramatically as the group size increases. Intriguingly, when we allowed all agents to deviate occasionally from the ideal path and choose a random path at each intersection, the congestion was significantly resolved. Specifically, the average time spent increased more slowly with the number of agents compared to that in the group following the ideal path. Moreover, by varying the probability of each agent choosing a random path rather than the navigated path, we found that there exists an optimal level of randomness that increases monotonically as the number of agents increases. Overall, our findings demonstrate the effectiveness of incorporating individual random behavior in multi-agent system optimization, thus providing insight into the possible benefits of random behaviors observed in humans and animals.

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**Poster**

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**Topic:** H.06. Social Cognition

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AMED-CREST 21gm1510003

**Title:** Differential and temporally-dynamic involvement of primate amygdala nuclei for social and reward information processing

**Authors: *K. KURAOKA**, K. NAKAMURA;
Dep.of Physiology, Kansai Med. Univ., Hirakata-Shi, Japan

**Abstract:** At a restaurant, we may perceive the same food differently when served by a robot clerk or by a real person clerk. Our decision-making is thus influenced by the expected appetitive and aversive outcomes but is also influenced by social aspects, such as who offered the outcomes. Among many brain areas which have been implicated in valence coding, the amygdala is also implicated in processing social information. However, it is still being determined whether they are computed separately or conjointly. To this end, we had two macaques make saccades to a target presented on the left or right of a central fixation point (FP), under different social and reward contexts. The context was created by presenting one of eight images with two attributes, social reality: a monkey or cartoon face, and reward: large or small. The image was presented twice in a trial, after an FP (S1) and before saccades (S2). During S2, half of the faces always gazed toward (congruent) and the other half always gazed away from (incongruent) the future target. Thus, visual images carried information about social reality (real monkey or cartoon face), the expected amount of rewards (large or small), and congruency of gaze direction and saccade targets. We found that neurons in the distinct amygdala sub-nuclei encoded social reality and reward information separately, with distinct temporal dynamics. As a population, the lateral nucleus (La) neurons responded stronger to monkey- than cartoon- faces during the S1. The basal (Ba) and central (Ce) nuclei neurons showed stronger responses to large- than small-reward-associated faces. The reward-dependent modulation was characterized by a continuous time course but was more conspicuous during the S1 in the Ba and during the S1 and S2 in the Ce. In all sub-nuclei, neurons modulated solely by a social or a reward factor, and those modulated by both factors coexisted. Some neurons in La showed a stronger response to incongruent than congruent stimuli, supporting its involvement in social information analyses. These results indicate anatomically- and temporally- distinct social reality and reward information processing: La's social reality, Ba's reward information at the sensory encoding phase, and Ce's continuous reward information processing.

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**Poster**

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**Topic:** H.06. Social Cognition

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**Title:** A subanesthetic dose of (R,S)-ketamine induces an aversion to harming a cage mate in rats

**Authors: *E. M. HESS**, T. D. GOULD;
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**Abstract:** There is currently no pharmacotherapeutic that alleviates dysfunction in the ability to perceive and understand the emotions of another i.e., affective perspective taking (APT) which is a core aspect of empathy. While the complexities of human empathy are difficult to model in rodents, behavioral paradigms utilizing rats which study decision making in social contexts may provide a translational framework for assessing biological, pharmacotherapeutic, and environmental interventions. The objective of this study was to assess the efficacy of the rapid-acting antidepressant (*R,S*)-ketamine in the harm aversion task (HAT); a behavioral paradigm that models APT in rats. The HAT measures the willingness of rats to forego pressing a lever to receive a sucrose pellet in order to prevent their cage mate from receiving an electric shock. Same-sex pair-housed adult rats (P90; n=47 male pairs, n=40 female pairs) were assigned as either the observer, which had access to the lever, or the demonstrator, which would receive shocks. After training the observer to press the lever to receive sucrose pellets, the demonstrator was placed into an adjacent chamber at which point lever responses would also deliver a shock. If the observer did not press the lever, no shock and no sucrose was delivered. Seven daily testing sessions were conducted with treatment occurring after the first session. An overall sex difference in harm aversion was observed in untreated rats with males (n=18) displaying greater aversion to harming their cage mate relative to females (n=15). A sub-anesthetic dose of (*R,S*)-ketamine (10 mg/kg s.c.; n=15 males, n=13 females) ameliorated this sex difference and increased harm aversion overall relative to saline-treated controls (n=14 males, n=12 females). Additionally, relative to controls, (*R,S*)-ketamine treated rats displayed lower activity counts within the reward tray immediately following shock delivery to their cage mate, suggesting they chose to investigate their cage mate over obtaining the sucrose reward. Thus, (*R,S*)-ketamine facilitates harm-aversion. This increased willingness to forego personal gain in order to protect their cage mate could be via strengthening APT in rats. Dysfunction in APT is observed as an endophenotype in various spectrum disorders including autism, for which (*R,S*)-ketamine may be an effective therapeutic. Further work is required to assess the neural mechanisms underlying this finding.

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**Poster**

**PSTR050. Animal Behavior and Social Cognition I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR050.06/RR4

**Topic:** H.06. Social Cognition

**Support:** RGPIN-2018-04699

**Title:** Estrogen but not androgen receptors modulate social recognition by interacting with the AVP system in male mice

**Authors: *D. ASPESI**, S. MATTA, T. MANNING, A. VARATHARAJAH, E. RECHTORIS-MCNAB, E. CHOLERIS;
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**Abstract:** The infusion of testosterone (T), 17β-estradiol (E2), or dihydrotestosterone (DHT) into the bed nucleus of the stria terminalis (BNST) of adult castrated (CX) male mice rapidly facilitated Social Recognition (SR). Next we sought to identify the specific steroid receptors involved, either androgen (AR) or estrogen receptors (ERs). Adult male mice were bilaterally injected into the BNST with CRISPR/Cas9-containing AAVs to selectively Knock Down (KD) either the AR, ERα, ERβ or G protein-coupled estrogen receptor (GPER). After 4 weeks, mice were CX and implanted with bilateral cannulas targeting the BNST to allow infusion (10-14 days later) of doses of T, E2, DHT previously shown to facilitate SR. Fifteen minutes after infusion, mice were tested in a "difficult" SR paradigm, in which CX mice are impaired. The results of this experiment revealed that ERα and/or ERβ are each required for the rapid facilitation of SR by T and E2 in the BNST, whereas DHT facilitates SR through the AR. Surprisingly, GPER KD did not affect SR facilitation by any of the steroids. The BNST contains steroid-regulated vasopressinergic (AVP) neurons that project to the lateral septum (LS). Previous work found that a subeffective (that per se does not block SR) dose of a selective AVP 1a receptor antagonist (V1aRA) in LS can block the facilitating effects of T and E2, but not those of DHT, on SR. To identify the specific ER involved in this Estrogen/AVP interaction, male CX mice received the infusions of V1aRA into the LS just before effective doses of PPT (ERα agonist) or DPN (ERβ agonist) into the BNST. The facilitative effects on SR of both PPT and DPN were blocked by infusion of V1aRA into LS demonstrating the rapid interaction between each of these ERs and AVP neurons in the BNST-LS circuit. These results also suggest that T is mainly converted to E2 into the BNST and, by binding ERα and ERβ, modulate the activity of AVP neurons projecting to the LS. Instead, the AR drives the rapid facilitating effects of DHT on SR through non V1aR-dependent mechanisms yet to be understood. Identifying the mechanisms involved in the rapid modulation of social behavior by AR and ERs may lead to new therapeutic approaches for psychopathologies of social behavior with marked sex differences.

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**Poster**

**PSTR050. Animal Behavior and Social Cognition I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR050.07/RR5

**Topic:** H.06. Social Cognition

**Support:** CIHR Grant 179866

**Title:** Sex differences in individual recognition of familiar conspecifics in C57BL/6 mice

**Authors: A. LAROSA**[1], J. Q. LEE[1], J. ZHU[1], A. WONG[1], M. BRANDON[2], *T. WONG[1,2]; [1]Douglas Res. Ctr., Verdun, QC, Canada; [2]Psychiatry, McGill Univ., Montreal, QC, Canada

**Abstract: Introduction:** Social memory, or the ability to recognize individuals, is critical to the survival of social animals. Impairments may underlie social behavior deficits in conditions such as autism spectrum disorder where an estimated one third of adults have difficulties in face individual identity recognition. Social memory tests in rodents are commonly based on novelty where recognition is determined by the subject's preference to interact with a novel, rather than a familiar, target. However, this method depends on the categorical recognition of novelty and not individual recognition. To our knowledge, individual recognition tasks which allow for the inclusion of both sexes, are ethologically relevant and easily replicable across laboratories do not exist. **Methods:** We developed paradigms to test individual recognition for two familiar social targets using C57BL/6 mice. Subjects were trained through multiple interactions with two sex-matched social targets: a neutral mouse and a mouse associated with a negative experience. The aversive experience was either attacks from an aggressive mouse or electric shocks presented during interactions with one of the social targets. Following experiences with the neutral and agonist or shock-associated mouse, interaction time was measured in a social discrimination test. **Results:** Male mice spent less time interacting with the agonist ($n = 22$, $p = 0.023$) and shock-associated ($n = 31$, $p = 0.002$) mice compared to neural targets. Males that were not previously exposed to either social target, exposed to both targets in the absence of aversive stimuli, or who were tested with novel social targets were used as controls to confirm that the decrease in interaction was specific to the agonistic and shock-associated social targets. This decrease was not observed in female mice (attack conditioned: $n = 14$, shock conditioned: $n = 32$). However, in a social novelty preference test males and females preformed similarly in their ability to identify novel social targets. **Conclusions:** Female C57BL/6 mice can identify novel social targets to a similar extent as males but perform poorer in tests of individual recognition. Attack and shock conditioning may be used to examine neural mechanisms of individual recognition, sex differences, and impaired recognition in conditions, such as autism spectrum disorder and schizophrenia, in brain regions critical to social memory.

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**Poster**

**PSTR050. Animal Behavior and Social Cognition I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR050.08/RR6

**Topic:** H.06. Social Cognition

**Title:** A normative theory of social conflict

**Authors: *S. SHUVAEV**[1], E. AMELCHENKO[2], D. SMAGIN[3], N. KUDRYAVTSEVA[3], G. ENIKOLOPOV[2], A. KOULAKOV[1];
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**Abstract:** Social hierarchy in animal groups carries a crucial adaptive function by reducing conflict and injury while protecting valuable group resources. Social hierarchy is dynamic and can be altered by social conflict, agonistic interactions, and aggression. Understanding social conflict and aggressive behavior is of profound importance to our society and welfare. In this study, we developed a quantitative theory of social conflict. We modeled individual agonistic interactions as a normal-form game between two agents. We assumed that the agents use Bayesian inference to update their beliefs about their strength or their opponent's strength and to derive optimal actions. We compared the results of our model to behavioral and whole-brain neural activity data obtained for a large population of mice engaged in agonistic interactions. We find that both types of data are consistent with the first-level Theory of Mind model (1-ToM) in which mice form both "primary" beliefs about their and their opponent's strengths as well as the "secondary" beliefs about the beliefs of their opponents. Our model helps identify brain regions that carry information about these levels of beliefs. Overall, we both propose a model to describe agonistic interactions and support our quantitative results with behavioral and neural activity data.

**Disclosures: S. Shuvaev:** None. **E. Amelchenko:** None. **D. Smagin:** None. **N. Kudryavtseva:** None. **G. Enikolopov:** None. **A. Koulakov:** None.

**Poster**

**PSTR050. Animal Behavior and Social Cognition I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR050.09/Web Only

**Topic:** H.06. Social Cognition

**Support:** NSERC 311637
NSERC PDF-546008-2020

**Title:** Socially inexperienced adult zebrafish find animated social stimulus less rewarding

**Authors: *S. SHAMS**[1], R. T. GERLAI[2];
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**Abstract:** Following the COVID19 pandemic, the need to understand behavioural and physiological effects of long-term and developmental social isolation is more evident than ever. Zebrafish behavioural research has shown immense potential for modeling neuropsychiatric diseases, particularly neurodevelopmental disorders and social deficits. When presented with a live or animated social stimulus, zebrafish typically move closer to the stimulus (within 10 cm) and this reduction in social distance is associated with the dopaminergic system. Groups of socially-naive isolated fish exhibit abnormally greater distances between shoal-mates but it is unclear whether this social deficit results from abnormal visual or social processing due to developmental isolation itself or because socially inexperienced isolated fish serve as suboptimal and less attractive social stimuli for each other. To differentiate between the two possibilities, our goal was to examine the behavioural and physiological responses of isolated zebrafish to animated social stimuli that have been validated as attractive social stimuli and only provide visual information after life-long deprivation of visual social cues. We compared socially-naive and socially-experienced adult zebrafish (mixed sex, 6-months of age, n = 10-13 for each group) while presented with animated social stimulus and found that socially-naive isolated fish responded to the animated fish stimulus by reducing distance to the presentation side as well, but did not remain close afterwards as socially experienced fish do. Also, despite the robust behavioural response, animated stimulus presentation did not affect levels of neurotransmitter dopamine, its metabolite (3,4-Dihydroxyphenylacetic acid, DOPAC), and physiological stress marker, cortisol, in isolated fish, indicating that developmental social isolation has dynamic and lasting effects on social function. The identified behavioural and physiological differences between socialized and isolated fish can be exploited to further understand visual social processing during zebrafish social behaviour and its regulation in zebrafish models of neuropsychiatric disorders.

**Disclosures: S. Shams:** None. **R.T. Gerlai:** None.

**Poster**

**PSTR050. Animal Behavior and Social Cognition I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR050.10/RR7

**Topic:** H.06. Social Cognition

**Support:** NSERC Grant 400212

**Title:** Gonadal hormone regulation of social learning: Interactions with dorsal hippocampal D2-type dopamine receptors in male and female mice

**Authors: *N. BASS**[1], S. MCGUINNESS[2], E. CHOLERIS[3];
[1]Univ. of Guelph, Thornhill, ON, Canada; [3]Elena Choleris, [2]Univ. of Guelph, Guelph, ON, Canada

**Abstract:** Social learning, or learning by watching or observing others, is a critical tool used in numerous species to help navigate complex social environments. The underlying neurobiological mechanisms of social learning are poorly understood and may be tested using the social transmission of food preference (STFP) paradigm. The STFP has implicated the dorsal hippocampus (DH), the dopamine (DA) system, and sex hormones in social learning. We previously showed that DH infusions of a D2-type DA receptor antagonist blocked social learning in gonadectomized (GDX) but not gonadally intact male and female mice, suggesting that DH D2-type DA receptors interplay with gonadal hormones to regulate social learning. The *specific* hormones at play remained unknown. Here, we GDX animals and replaced hormones one at a time to determine whether they could protect against the impairing effects of DH D2-type DA receptor antagonism on social learning. In males, gonadal testosterone may act at androgen receptors or at estrogen receptors following aromatization to estrogens. In study 1, adult castrated (CAS) male "observer" (OBS) mice received subcutaneous long-term estradiol benzoate (EB) or vehicle (VEH) silastic capsules (experiment 1), or dihydrotestosterone (DHT), a potent androgen, or VEH capsules (experiment 2). In study 2, ovariectomized (OVX) female mice received subcutaneous long-term EB or VEH silastic capsules. In study 3, CAS (experiment 1) and OVX (experiment 2) OBS received long-term subcutaneous slow releasing progesterone or VEH pellets. In all studies, after 10 days of continuous hormone replacement, GDX OBS received bilateral infusions of the D2-type DA receptor antagonist raclopride (20 µg/µL for males or 18 µg/µL for females) into the DH 10-minutes prior to a 30-minute social interaction with a recently fed, same-sex, familiar "demonstrator" (DEM). Then, OBS underwent an 8-hour choice test between two novel flavored food diets. When social learning occurs, the OBS prefers the DEM diet. In all studies, long-term hormone replacement protected against the impairing effects of DH D2-type DA receptor antagonism on social learning. Findings from these studies will help elucidate the hormonal regulation of the social brain via interactions with neurotransmitter systems. Funded by NSERC.

**Disclosures:** **N. Bass:** None. **S. McGuinness:** None. **E. Choleris:** None.

**Poster**

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**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR050.11/RR8

**Topic:** H.06. Social Cognition

**Support:** NFRF Grant NFRFE-2021-00936

**Title:** Changes in social environment impact primate microbiome composition

**Authors:** ***C. S. PEARCE**[1,2], D. BUKOVSKY[1], K. DOUCHANT[3], C. SJAARDA[2], P. SHETH[3,2], V. KUHLMEIER[1], M. SABBAGH[1], G. BLOHM[2], F. DE FELICE[2,3], M. PARE[3], D. J. COOK[4,2], S. H. SCOTT[3,2], D. P. MUNOZ[3,2], A. TUSCHE[1], D. J. GALE[2], S. E. BOEHNKE[2,3], A. WINTERBORN[2], J. P. GALLIVAN[1,2];
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**Abstract:** Composed of trillions of microbes, the gut microbiome, also known as the "forgotten organ," is essential for health and wellbeing. Contemporary neurobiological studies underline its profound impact on cognition and behavior through the brain-gut-microbiome axis, with dysfunctions in this pathway having been linked to various health problems, including heart disease, cancer, and depression. Yet, the forces that ultimately shape the gut microbiome remain opaque. Perhaps the most poorly understood, yet potentially most consequential of forces that can shape the gut microbiome is one’s social environment. Work in humans and nonhuman primates has suggested that cohabitation and frequent social interaction are responsible for similarities in gut microbiome composition. In turn, these studies have noted changes in behavioral and cognitive functioning as a result of these microbiota shifts. However, it is difficult to assess causation in these studies, and interpretations are complicated by the influence of uncontrolled but correlated factors known to directly impact the gut microbiome, such as diet. Here, we performed an investigation of the impact of changes in social environment on gut microbiome composition in a cohort of male cynomolgus macaques (Macaca fascicularis, ages 7 - 9yrs) while controlling for diet. Our longitudinal study design tracked 13 captive males through three 6-month phases of social living conditions (single housing to divided social living and back to single living) over an 18-month period, during which we collected feces and hair samples to assess changes in gut microbiome composition and systemic cortisol levels, respectively. We found that social living conditions significantly increased animals’ cortisol levels, consistent with a physiological stress response associated with increased social interactions in males. Concomitant with these physiological effects, we also observed changes in gut microbiome composition above and beyond what could be explained by diet alone, indicating a direct effect of changes in social environment on gut biodiversity. Together, these findings suggest that changes in sociality can impact the physiology of primates at multiple biological levels, which may underlie the known relationship between social environment and individual wellbeing.

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**Poster**

**PSTR050. Animal Behavior and Social Cognition I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR050.12/RR9

**Topic:** H.06. Social Cognition

**Support:** NSERC
Brain Canada
CIHR

**Title:** Hypocretin Neuron Activity is Required for Male Social Interaction and Disrupted by Social Isolation

**Authors: *M. K. DAWSON**[1], D. J. TERSTEGE[2], N. F. JAMANI[1], M. TSUTSUI[1], V. LEE[3], K. MURARI[3], J. R. EPP[2], D. SARGIN[1];
[1]Psychology, [2]Cell Biol. and Anat., [3]Electrical and Software Engin., Univ. of Calgary, Calgary, AB, Canada

**Abstract:** Chronic social isolation during adolescence disrupts normal social behavior and is a risk factor for anxiety and depression. Proper social functioning during adolescence is also essential for development of adult social behavior. Yet, our knowledge of which brain regions and circuits are affected by social isolation is incomplete. Based on our previous work (Dawson et al., 2023), the activity of hypocretin neurons - a cluster of neurons endemic to the lateral hypothalamus that govern arousal and motivation - is essential for normative social behavior. Our project builds on these findings to test our hypothesis that chronic social isolation produces deficits in social interaction by disrupting the normal functioning of hypocretin neurons. To do this, we first performed *in vivo* calcium recordings from hypocretin neurons in female and male control (group-housed) and isolated (single-housed) mice and examined the differences in hypocretin activity during social interaction. We quantified social interaction behavior using an automated behavioral classifier. Here, we show that hypocretin neuron activity increases in female and male control and isolated mice upon initial interaction with a same-sex stranger conspecific. However, the amplitude of interaction-induced hypocretin activity is significantly reduced in female and male isolated mice, compared with controls. Quantification of social behavior showed that isolated mice displayed deficits in social interaction when compared with control mice. Next, we used a social fear conditioning paradigm to examine how chronic social isolation influences social valence learning. To assess the interaction between chronic social isolation and induced social fear, we performed fiber photometry in conditioned control and isolated mice during a social interaction assay. These experiments elucidate how hypocretin neuron activity is modulated with social anxiety and provides the framework for targeted stimulation to overcome social deficits.

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**Poster**

**PSTR050. Animal Behavior and Social Cognition I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR050.13/RR10

**Topic:** H.06. Social Cognition

**Support:** This work was carried out within the framework of the project "RAISE - Robotics and AI for Socio-economic Empowerment" and has been supported by European Union - NextGenerationEU
Marie-Curie project LgDel-mPFC (EPUE038401)

**Title:** A SiNAPS research platform for behavioral studies with implantable CMOS probes

**Authors: C. STUBBENDORFF**[1], J. RIBEIRO[1], G. ORBAN[1], *M. VINCENZI[2], A. PERNA[1], G. N. ANGOTZI[3], L. BERDONDINI[4];
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**Abstract:** Implantable neural probes based on SiNAPS technology offer the capability of monitoring large brain ensembles at cellular resolution in animal models. Integrating this probe technology in smart systems for behavioral studies in freely moving animals provides an unprecedented opportunity to investigate the electrophysiological correlates of animal behaviour. Toward this objective, we designed and realized a platform enabling chronical implantation of SiNAPS probes in freely behaving mice monitored by video imaging. For the implant we took advantage of the very small footprint of single-shank 256 electrodes SiNAPS probes and integrated these devices on a small form factor (1.7 cm2) printed circuit board (PCB). The total weight is less than 3 g. A custom interconnecting cable (19 wires in total) is connected from the probe to a commercial commutator, which provides the electrical connectivity to an FPGA-based instrument for data acquisition and device control. The same FPGA generated control signals for the video cameras, thus ensuring a synchronous recording of neural electrical data and behavioral video data. Results show preliminary results demonstrating the stability of recordings collected from chronically implanted SiNAPS probes and of the functionality of acquiring multimodal data from mice. Implantation procedures and devices were also assessed with respect to the possibility of keeping multiple implanted animals in the same cage. These results pave the way for studies on neurodynamics at the mesoscale in freely moving animals and disease models.

**Disclosures: C. Stubbendorff:** None. **J. Ribeiro:** None. **G. Orban:** None. **M. Vincenzi:** None. **A. Perna:** None. **G.N. Angotzi:** None. **L. Berdondini:** None.

**Poster**

**PSTR050. Animal Behavior and Social Cognition I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR050.14/RR11

**Topic:** H.06. Social Cognition

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Berettler Centre for Research in Molecular Pharmacology and Therapeutics Grant
Satell Family Foundation
Neubauer Family Foundation

**Title:** Nitric oxide: A novel therapeutic target for Cntnap2 mouse model of autism spectrum disorder

**Authors: *M. KARTAWY**[1], M. K. TRIPATHI[2], W. HAMOUDI[2], S. OJHA[2], H. AMAL[2]; [1]Hebrew Univ. of Jerusalem, Jerusalem, Israel; [2]The Sch. of Pharm., Hebrew Univ., Jerusalem, Israel

**Abstract:** Core behavioral deficits of autism spectrum disorder (ASD) have been reported in humans with *CNTNAP2* mutations. *CNTNAP2* gene encodes a neuronal transmembrane protein member of the neurexin superfamily, which is involved in neuron-glia interactions and clustering of $K^+$ channels in myelinated axons. The *Cntnap2* knockout mice exhibit an ASD-like behavioral phenotype. Among the numerous signaling molecules of the central nervous system (CNS), nitric oxide (NO•) occupies a special place in the brain. At low concentrations, NO• serves as a signaling molecule, taking part in the regulation of synaptic activity, synaptic plasticity, and vesicle trafficking. However, at high concentrations, NO• might be toxic, possibly leading to modified phenotypes and cell death. It has been reported that NO• plays a role in neurodegenerative diseases. However, little is known about the role of NO• signaling and S-nitrosylation (SNO, the NO-mediated posttranslational modification) in neurodevelopmental disorders (NDDs), including ASD. In this study, we tested the hypothesis that a mutation in the *Cntnap2* gene in mice induces an increase in NO• production, leading to nitrosative stress that ultimately converges into synaptic and behavioral deficits. Our results show significantly elevated levels of 3-nitrotyrosine in the cortex of the *Cntnap2* mutant mice, indicating both oxidative and nitrosative stress. To this end, the *Cntnap2*$^{-/-}$ mice were treated with a selective inhibitor of neuronal NO synthase (nNOS). Follow-up experiments were conducted to examine the potential effects of inhibiting NO• signaling on molecular, synaptic, and behavioral phenotypes. Administering nNOS inhibitor to *Cntnap2*$^{-/-}$ restored the expression levels of synaptophysin, a marker of synaptogenesis. The treatment also led to a significant increase in the dendritic spine density in the somatosensory cortex of the mutant mice. Moreover, the treatment resulted in the restoration of Glutamatergic (NR1) and GABAergic (Gad1 and Vgat) markers levels. Furthermore, the pharmacological intervention led to a reversal in the social deficits, anxiety-like behavior, and an increase in novelty-seeking in the mutant mice. These findings provide compelling evidence that NO• plays a key role in ASD associated with the *Cntnap2* mutation. Targeting NO• signaling is a promising therapeutic approach for ASD.
**Keywords**: autism spectrum disorder, nitric oxide, synaptogenesis, behavioral dysfunction, excitatory/inhibitory neurotransmission.

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rights/patent holder, excluding diversified mutual funds); We have patent owned by the Hebrew University and liscneced by Pharma Company: Title: METHODS AND PHARMACEUTICAL COMPOSITIONS FOR TREATING NEUROLOGICAL CONDITIONS. Other; Only Research grants funded our project. Recently the Hebrew university signed a research agreement with a public company (name still confidential).

**Poster**

**PSTR050. Animal Behavior and Social Cognition I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR050.15/RR12

**Topic:** H.06. Social Cognition

**Title:** Understanding Dyadic Processes in a Rat Observational Learning Model

**Authors: *T. WRENN**, R. TROHA, N. ANNADURAI, A. PAXTON, E. J. MARKUS; Psychological Sci., Univ. of Connecticut, Storrs, CT

**Abstract:** Observational learning can be defined as a change in behavior that follows the observation of another performing a task rather than personally performing the task. From an evolutionary aspect, it is beneficial to learn from a conspecific rather than expending energy or exposing oneself to danger during trial-and-error learning. Our lab has developed an observational learning paradigm, with two conjoined operant chambers. “Learner rats” must attend to watch a “teacher rat” in the other chamber respond at one nose poke and then choose the corresponding nose poke in their own chamber. The behaviors of both the teacher, learner and their interactions are tracked and related to the trial’s success or failure. The automated nature of this task allows for multiple trials per session and results in rapid social learning. The current task encompasses 80 observation trials per session, allowing for an in-depth analysis of the behaviors. In addition, precise behavioral assessment of both the learner and teacher rats is possible through a machine learning assisted program, DeepLabCut (Mathis et al., 2018). Performance of the learner is measured, as well as distance and heading orientation to the teacher throughout the task. While successful observation is of course based on the behavior of the learner rat, the behavior of the teacher rat is also important. Therefore, we also determined what behavioral characteristics of the teacher rat facilitated successful observational learning. To accomplish this, we use a variety of teachers and see which animals and behaviors are related to better performance in the learners. Traditional approaches to understanding successful observation, such as proximity, location and orientation will be used. In addition, we will also monitor dyadic interactions using a recurrence quantification analysis (RQA). This will further extract and differentiate behaviors related to successful and unsuccessful learning in the dynamical processes of social learning in rats.

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**Poster**

**PSTR050. Animal Behavior and Social Cognition I**

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**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR050.16/RR13

**Topic:** H.06. Social Cognition

**Support:** PRIN 2017 KZNZLN_004
ERC 648734 HUMO

**Title:** Neural Correlates of Observational Learning in the Macaque Dorsal Premotor Cortex during a Human-Monkey Interactive Associative Task

**Authors: *F. CECCARELLI**[1], L. FERRUCCI[1], S. NOUGARET[2], F. LONDEI[1,3], G. ARENA[1,3], A. GENOVESIO[1];
[1]Physiol. and pharmacology "Vittorio Erspamer", La Sapienza, Roma, Italy; [2]Aix-Marseille Univ. & CNRS, Aix-Marseille Univ. & CNRS, Marseille, France; [3]PhD program in Behavioral Neuroscience, Sapienza Univ., Rome, Italy

**Abstract:** Primates have a complex social life that requires monitoring and understanding the actions and choices of the other group members and learning from others' behavior. While prior behavioral studies have shown monkeys' remarkable observational learning abilities, how the information learned by observation is encoded at the neural level has not been studied yet. In this study, we recorded single-unit activity in the dorsal premotor cortex (PMd) while two macaque monkeys performed a human-monkey interaction version of an associative learning task, the "object-in-place" (OIP). In the OIP task, the monkeys were presented with four associative problems, wherein two objects, one rewarded and one unrewarded, were consistently positioned in the same positions within a scene characterized by a unique background. The human actor interacted with the monkey sitting next to the monkey and performing the task while observed by the monkey. Each trial started with a central target (CT) to be held by the monkey/ human actor until the problem was presented and the delay period started. Thereafter, the CT turning off acted as a "go" signal to touch the chosen object. Once the touch on the selected object was maintained for a "pre-feedback" period, a visual feedback around the object appeared for a feedback period. In each recording session, we introduced a set of four novel problems. Initially, during the Learning period (LP), the monkey observed the human actor performing the task correctly in the first 60 trials, where all four problems were presented for the first time. Subsequently, in the Test period (TP), the monkey's ability to learn the correct object of each problem by observation was assessed in 15 trials. Finally, during the Interaction period (IP), the monkey and human took turns performing the task until the session ended. Both monkeys completed the TP without errors, providing compelling evidence that they had learned the correct object associated with each observed scene. Applying a decoding approach, we investigated the ability of the PMd neural population to represent the human's forthcoming action during the delay period across the LP and IP periods. The representation of human action started to increase during learning from the late stage of the LP period to reach its peak in the later IP period. These findings indicate the

involvement of the PMd not only in individual learning but also in associative learning through observation.

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**Poster**

**PSTR050. Animal Behavior and Social Cognition I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR050.17/RR14

**Topic:** H.06. Social Cognition

**Title:** Reconfiguration of the network activity during goal-action transformation in primate frontal cortex studied at the cell assembly level

**Authors: *F. LONDEI**[1,2], F. CECCARELLI[1], G. ARENA[1,2], L. FERRUCCI[1], A. GENOVESIO[1];
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**Abstract:** Cell assemblies are functional clusters of neurons with a specific temporal firing pattern and with distinct information-encoding properties. We studied the formation of cell assemblies in the macaque prefrontal and premotor cortex using a temporal and a distance discrimination task requiring to discriminate either the farthest from screen center or the longest stimulus of two stimuli presented sequentially, respectively. After the presentation of the second stimulus, there was a delay period followed by the presentation of the two stimuli on the right and left sides of the screen that acted as the go-signal. Only after the go-signal the memory of the stimulus with the highest magnitude (the goal) could be transformed into the action for selecting it. We studied the network reconfiguration after the go-signal examining the assembly activation of simultaneously recorded neurons. From the overall neuronal activity, we extracted the spikes fired during each assembly activation (assembly-spikes), which were compared to the full spiking activity (all-spikes). Interestingly, we found that a single neuron can participate in multiple assemblies, potentially encoding different variables or even the same variable but with a different coding preference. Thus, while a neuron has fixed coding properties, new properties emerge when considering its involvement in different assemblies. These properties encompass multiplexing, flexibility, and multiple selectivity, resulting in distinct neural responses depending on the specific assembly in which a neuron coordinates its activity. In a previous study on the same dataset, we described neurons switching goal preference in the transition between the pre- and post-go epochs that could indicate a network reconfiguration. To test the reconfiguration hypothesis, we quantified the participation of neurons in different assemblies. We found that even considering only neurons with a similar above-baseline activity in the two epochs in terms of all-spikes, 18% (compared to 2% in control epochs) of neurons were active with their assembly spikes either before or after the go-signal in different assemblies showing a full

reconfiguration. This result suggests that information was transferred from the network maintaining the goal in memory to the network involved in action execution. We also estimated how many neurons have at least a partial reconfiguration, where neurons are active in an assembly in only one of the two epochs. In this case, the percentage increases to 85% (compared to 45% in control epochs). These results provide evidence for a network reconfiguration during the goal-action transformation.

**Disclosures:** **F. Londei:** None. **F. Ceccarelli:** None. **G. Arena:** None. **L. Ferrucci:** None. **A. Genovesio:** None.

**Poster**

**PSTR050. Animal Behavior and Social Cognition I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR050.18/RR15

**Topic:** H.06. Social Cognition

**Title:** Neuronal population dynamics and network organizations reflect motivational context in monkey premotor cortex during movement execution and inhibition

**Authors: *V. GIUFFRIDA**[1,2], I. B. MARC[1], G. BARDELLA[1], S. RAMAWAT[1], R. FONTANA[1], E. BRUNAMONTI[1], P. PANI[1], S. FERRAINA[1];
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**Abstract:** Actions require constant updating of response preparation, which may involve suppressing or executing the action depending on context. Many studies have shown that the dorsal premotor cortex (PMd) is a key area for controlling the level of movement preparation. However, it is still unclear how contextual information is integrated to regulate movement preparation. To address this issue, we investigated the neuronal population dynamics and network organization in different motivational contexts. We recorded neuronal activity from PMd of two monkeys (Macaca mulatta), performing a a stop-signal reaching task. The task required to respond to a Go signal as fast as possible (Go trials), and to inhibit the response if an unexpected Stop signal (Stop trial) was presented. Before each trial, a Cue signal indicated in which motivational context (Go+: higher reward for correct Go than Stop trials; Stop+: higher reward for Stop than Go trials; Neutral: same amount for both correct trials) the current trial would run. We used spike density function (SDF) to perform neuronal analysis on well-isolated single unit activity. We extracted the neuronal dynamic by mapping the neuronal population activity in a Low-Dimensional State Space using a Principal Component Analysis (PCA). We also investigated the multiscale network topology by using the node-based multifractal analysis framework (NMFA) and minimal spanning tree analysis (MST). Behavioral results show that in both animals (M1 sessions=2; M2 sessions=5) the motivational context affected motor preparation by lengthening response times (RT) and increasing the ability to inhibit in the Stop+ condition compared to the Go+ condition. Analysis of the neuronal state space showed that in Go

trials of the Stop+ and Neutral conditions, the neural trajectories from the Go signal to motion generation evolved similarly, while in the Go+ condition, the trajectories followed a different evolution. The functional network analysis revealed that PMd has a more complex organization when deciding to stop than when deciding to move in the Go+ condition. However, this difference in complexity wasn't present in the Stop+ and Neutral conditions. The MST identified the topological backbone of the network revealing a network endowed have with hubs present the Go+ condition in both trial types, absent in the other conditions with a more dispersed functional communication between neurons. These results indicate that the motivational context influences the movement preparation in PMd. At neuronal level, these influences can be detected as changes in the neuronal dynamics, as well as in the complexity and topological organization of the network.

**Disclosures: V. Giuffrida:** None. **I.B. Marc:** None. **G. Bardella:** None. **S. Ramawat:** None. **R. Fontana:** None. **E. Brunamonti:** None. **P. Pani:** None. **S. Ferraina:** None.

**Poster**

**PSTR050. Animal Behavior and Social Cognition I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR050.19/RR16

**Topic:** H.06. Social Cognition

**Support:** Progetti H2020 - Collaborativi - Sapienza University N. PH120172B9427FA1

**Title:** Local field potentials in macaque dorsal premotor cortex are modulated by the manipulation of acquired ordinal information in a transitive inference task

**Authors: *I. B. MARC**[1,2], V. GIUFFRIDA[1,2], S. RAMAWAT[1], M. ANDUJAR[1], G. BARDELLA[1], P. PANI[1], S. FERRAINA[1], E. BRUNAMONTI[1];
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**Abstract:** Transitive reasoning provides us with the ability to decide among alternatives by connecting previously learned knowledge on an abstract mental representation. We experimentally investigated the neuronal correlates of this ability by recording, through a 96-channels array, the neuronal activity of the dorsal premotor cortex (PMd) of two male macaque monkeys performing a computer-controlled version of the Transitive Inference task (TI). Monkeys had first to acquire, by trial and error, the rank order of pairs of adjacent items as, A>B, B>C, C>D, D>E, E>F (learning phase) of a set of ordered items as A>B>C>D>E>F, then they had to infer the ordinal relation between items never paired in the previous phase as BvsD or CvsE (test phase). In the test phase novel pairs were randomly intermingled with pairs of adjacent items presented during the learning. Both, a symbolic distance (SDe) and a serial position (SPe) effect typically characterize the behavioral outcome in the test phase. The SDe shapes the behavior by increased performance and shorter reaction times (RTs) between items

with different ranks than those with similar ranks (BvsE easier than BvsC), while the SPe characterizes the performance as decreased accuracy and longer RTs in comparing pairs of items in middle positions of the list than extreme ones (AvsB and EvsF is easier than CvsD). These behavioral effects are hypothesized to emerge, after the completion of the learning phase, once items adjacent ranks are arranged on a spatially organized mental schema. In the test phase, this schema is explored by inward scanning of the list, starting from the extreme items. In line with the hypothesized cognitive mechanisms, here we observed that the behavior of both monkeys was significantly shaped by the SDe and SPe. Accordingly, this behavioral modulation was reflected in the PMd average power of local field potential obtained through time frequency analyses, confirming an involvement of this brain area in the manipulation of the acquired mental schema. Interestingly, a reflection of the SPe and the corresponding modulation of it was not observed during the learning phase, suggesting these effects emerge only after the acquisition of a mental schema. Overall, our results are in line with the hypothesis that PMd processes the information for completing this task and that a learning process models the neuronal activity for accomplishing the task's demands.

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**Poster**

**PSTR050. Animal Behavior and Social Cognition I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR050.20/RR17

**Topic:** H.06. Social Cognition

**Support:** NSERC grant 194517-03

**Title:** Novel effects of social context on the N400 event-related brain potential

**Authors: *S. SINHA**[1], H. PANTECOUTEAU[3], U. HESS[4], M. KOSTOVA[5], J. DEBRUILLE[2]; [1]Integrated Program in Neurosci., [2]McGill Univ., Montreal, QC, Canada; [3]École Normale Supérieure, Lyon, France; [4]Humboldt Univ., Berlin, Germany; [5]UR Paragraphe, Univ. Paris 8 Vincennes-Saint-Denis, Paris, France

**Abstract:** Social N400 studies reported *larger* amplitudes of the N400 event-related brain potential (ERP) when participants had privileged information about the stimulus that needed to be set aside to build a common ground with a confederate. This was found when participants and the confederate viewed the same visual stimuli together while they were within the visual periphery of each other. However, it remains unclear whether these social N400s are primarily due to the participants' ability to see the confederate's stimulus or simply due to the other's presence. To test this, we ran a first study where images were presented to participants in the presence of a stranger (STs), such that none could see each other's stimuli. Prior to each block of image presentations, participants were announced whether the images would be identical or

different from those shown to the other. Due to the private stimulus presentation, they had no way to verify the truth of these announcement, which were untrue (i.e., inconsistent with reality) half of the times. Surprisingly, we found that these images evoked significantly *smaller* N400s ($p < 0.001$) in STs ($n = 29$) than in those who were alone ($n = 30$). Subsequently, we ran a second experiment ($n = 30$) using a within-subject design where the announcements were always true. This time, there was no reduced N400, failing to replicate our initial results. Currently, we are conducting a third experiment to investigate whether we can replicate the smaller N400s when the stimulus announcements are untrue. An absence of smaller N400s in this case would suggest that participants of the first experiment somehow realized the inconsistencies with the announcements, and developed a specific processing strategy that minimizes N400s. If this were the case, future studies involving noticeable deceptions should further explore this type of strategies. Conversely, if smaller N400 responses are observed, it would raise the possibility that being in an unknown social context can trigger late joint processing effects (Bouten et al., 2015; preprints: Haffar et al., 2018; Jeuland et al., 2022). These findings might bring new insights as to the functional significance of the N400. On the other hand, as the building of a common ground is likely to be impaired in psychiatric patients, these results could open a new avenue of research as to the mechanisms of these impairments.

**Disclosures:** **S. Sinha:** None. **H. Pantecouteau:** None. **U. Hess:** None. **M. Kostova:** None. **J. Debruille:** None.

**Poster**

**PSTR050. Animal Behavior and Social Cognition I**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR050.21/RR18

**Topic:** F.02. Neuroendrocrine Processes and Behavior

**Support:** NIMH Grant R01 MH125411

**Title:** Imaging Kappa Opioid Receptor Status in a Titi Monkey Model of Human Pair Bonding; a Positron Emission Tomography (PET) Study

**Authors: *J. P. PAULUS**, C. MANCA, A. J. D'ALMEIDA, A. J. CHAUDHARI, K. L. BALES, B. A. HOBSON;
Univ. of California, Davis, Davis, CA

**Abstract:** Social connectedness, such as pair bond relationships, is crucially important in the regulation of emotions. Despite separation from pair mates having significant effects on physical and psychological stress responses, the neurobiological mechanisms underpinning these phenomena are not well understood. The kappa opioid system has been proposed as an important pathway for mediating separation responses through the modulation of oxytocin (OT) release, however the spatial temporal interactions between KOR and pair bonding stressors remain unclear. Titi monkeys (*Plecturocebus cupreus*), a socially monogamous non-human primate,

provide a unique and novel model for investigating the role of KORs in separation because they enable rigorous, clinically relevant behavioral measures of separation distress. Given the differences in both opioid and OT receptor distributions between rodents and primates, it is unclear whether [$^{11}$C]GR103545 positron emission tomography (PET) will be an effective means to assess KOR occupancy in titi monkeys. In this study, we evaluated the feasibility of noninvasive [$^{11}$C]GR103545 PET to assess KOR receptor occupancy in titi monkeys. Six adult titi monkeys were imaged on a dedicated primate brain PET scanner (PiPET, Brain Biosciences) under baseline conditions and after administration of: 1) a KOR antagonist (LY2456302; 0.3mg/kg), and 2) a KOR agonist (U50,488; 3mg/kg). PET image data were motion-corrected and coregistered with a corresponding $T_1$-weighted brain MRI scan (1.5T HDxt scanner, General Electric) acquired for each subject. Image data were parcellated into anatomical regions of interest (ROIs) via non-rigid warping of a titi monkey brain atlas (46 brain regions) to each subject's MR scan. The non-displaceable binding potential ($BP_{ND}$) was calculated across ROIs using the Logan Reference Tissue Model. The blocking agents were well tolerated at administered doses. Compared to baseline scans, administration of LY2456302 significantly reduced radiotracer binding in oxytocinergic areas such as the hypothalamus ($p = .016$) and pituitary gland ($p = .031$) suggesting high sensitivity of [$^{11}$C]GR103545 to assess KOR occupancy. We observed significantly less reduction in tracer binding after application of U50,488. This discrepancy may be due to facets of the KOR specific to titi monkeys as variation in binding affinity to these compounds is seen across primates. Nonetheless, these results indicate [$^{11}$C]GR103545 PET is a powerful tool for monitoring KOR status in titi monkeys and will enable assessment of the KOR system concurrent with pair bonding behavioral assays.

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**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR051.01/RR19

**Topic:** H.06. Social Cognition

**Support:** NINDS F99/K00 1F99NS125826-01A1
NIMH T32 AG049688

**Title:** Anterior cingulate cortex neurons encode social identity during decision-making task

**Authors: *J. SIMON, IV**[1], E. L. RICH[2];
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**Abstract:** Processing social information is an important component of navigating our environment. Both humans and monkeys can use information coming from conspecifics, as an

alternative to nonsocial sources, to make decisions including threat detection or foraging. Yet, it is unclear if the processing of social information (i.e., eyes/faces), in comparison to nonsocial information, is encoded differently in the brain. Processing of this information has been linked to many brain regions including the anterior cingulate cortex (ACC), specifically the ACC gyrus. Here, we asked whether this region preferentially encodes information from a social source relative to a nonsocial source, particularly when the desired actions are the same. To test this, we trained two female rhesus monkeys to perform a reward localization task. The task required monkeys to use visual guides, either social or nonsocial, to locate a reward cue. Visual guides were divided into social images (i.e., pictures of monkey faces, gazing to the left or right) and nonsocial images (i.e., arrows on a complex background, pointing to the left or right). Monkeys had to use these visual guides to successfully locate a reward cue between two identical squares. During testing, we preformed acute neurophysiological recordings, targeting the ACC gyrus (N = 214). We also targeted the prearcuate cortex (PAC, N = 228), which includes the frontal eye fields, as this region has not been implicated in selectivity for social information. We found that monkeys were able to locate the rewarding target above chance levels (50%) and were significantly better at nonsocial images compared to social. Neither ACC nor PAC preferentially responded to social compared to non-social stimuli. However, in ACC there were more neurons that encoded unique social images, compared to nonsocial images, whereas this was not observed in PAC. Therefore, the ACC might contribute to social cognitive functions by tracking unique social identities.

**Disclosures: J. Simon:** None. **E.L. Rich:** None.

**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR051.02/RR20

**Topic:** H.06. Social Cognition

**Support:** NINDS T32 NS061788
MH-11856304
MH-11856304S1

**Title:** Hippocampal-prefrontal neuronal dynamics contributing to social memory deficits in a mouse model for Rett syndrome

**Authors: *D. MEDEIROS**, L. POZZO-MILLER;
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**Abstract:** Rett syndrome (RTT) is a neurodevelopmental disorder caused by loss-of-function mutations in the X-linked *MECP2* gene, affecting mostly females with a prevalence of 1:10,000 births. Social memory impairments and underlying circuit-level deficits have been demonstrated in the monosynaptic projection from the ventral hippocampus (vHIP) to the medial prefrontal

cortex (mPFC) of male *Mecp2* knockout (KO) mice, an established mouse model for RTT. This projection is also dysfunctional in neuropsychiatric disorders such as non-syndromic autism and schizophrenia. The hippocampal network is hyperactive in RTT mice, and such atypically heightened neuronal activity propagates to the mPFC through this monosynaptic projection, resulting in altered mPFC network activity and social memory deficits. However, the underlying mechanism of cellular dysfunction within this projection between vHIP pyramidal neurons (PYR) and mPFC PYRs and parvalbumin interneurons (PV-IN) resulting in social memory impairments in *Mecp2* KO mice has yet to be elucidated. We confirmed social memory deficits in *Mecp2* KO mice and wildtype (WT) controls using a novel 4-chamber social memory assay, where the test mouse is placed in the center chamber surrounded by 3 chambers separated by perforated plexiglass partitions. This novel arena is customized to reduce the impact of the optical fiber tethering required for *in vivo* neuronal recordings simultaneously with behavioral monitoring by reducing the distance that the test mouse needs to cover to interact with the surrounding chambers compared to the classical linear 3-chamber arena. We performed fiber photometry of the $Ca^{2+}$ sensor GCaMP8m expressed in mPFC excitatory PYR (*CamkII* promoter) and the $Ca^{2+}$ sensor FLEX-GCaMP8f expressed in mPFC of PV-Cre mice to characterize their respective activity during social interactions with novel and familiar mice. In addition, we performed structural analyses of vHIP synaptic inputs onto mPFC PYRs and PV-INs using near super-resolution confocal microscopy in *Mecp2* KO mice and WT controls. This work aims to elucidate underlying mPFC cellular populations that are targets of vHIP innervation, providing insight and potential therapeutic targets for psychiatric disorders associated with vHIP-mPFC dysfunction.

**Disclosures: D. Medeiros:** None. **L. Pozzo-Miller:** None.

**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR051.03/SS1

**Topic:** H.06. Social Cognition

**Support:** NIH R15 MH117611-01

**Title:** Neurophysiology of the degu, dorsal medial frontal cortex during social interaction

**Authors:** M. PILKIW[1], P. HANNI[3], K. TAKEHARA-NISHIUCHI[2], ***N. INSEL**[4];
[2]Dept. of Psychology, [1]Univ. of Toronto, Toronto, ON, Canada; [3]Univ. of Montana, Missoula, MT; [4]Wilfrid Laurier Univ., Waterloo, ON, Canada

**Abstract:** In mammalian brains, the dorsal medial frontal cortex includes regions of rostral cingulate and premotor cortex that have complimentary roles in task engagement and movement planning. While these regions have been implicated in social behavior, there has been an absence of integrative theories on function, propelling explorations linking neural activity with animals'

social-behavioral context. One challenge to using natural behavior is that social motivation and interaction differ widely between species, raising the need--and opportunity--to use comparative approaches that identify generalized principles of frontal computation, while also leveraging species' individual specializations. The present work examined neural activity patterns in dorsal medial frontal cortex and hippocampus in freely-moving degus during a series of social and non-social stimulus exposures. Degus, a caviomorph rodent native to Chile, are highly gregarious, show extended face-to-face greetings, and can exhibit cooperative behavior with unrelated peers. Preliminary observations from four degus reveal that neuron population activity and the local, 40 to 70 Hz gamma oscillation increased in the frontal cortex during social investigation relative to investigation of non-social objects. Population activity was higher around the onset of social interactions, though the activity of individual neurons was inconsistent within measured behavioral categories. Consistent with other rodents, hippocampal theta oscillations increased frequency with self-motion velocity, though only weak correlations were observed between hippocampal theta and frontal activity. These results contribute to our knowledge about the medial frontal cortex during social behavior and provide a step toward understanding mechanisms underlying the social behavioral dynamics of degus.

**Disclosures:** **M. Pilkiw:** None. **P. Hanni:** None. **K. Takehara-Nishiuchi:** None. **N. Insel:** None.

**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR051.04/SS2

**Topic:** H.06. Social Cognition

**Support:** KAKENHI-PROJECT-23KJ1559

**Title:** Processing of social information via inhibitory neurons in the insular cortex

**Authors:** ***S. FUJIMA**[1], M. SATO[2], N. NAKAI[3], T. TAKUMI[4];
[1]Kobe Univ., Hyogo, Japan; [2]Hokkaido Univ. Grad Sch. Med., Hokkaido Univ., Sapporo, Hokkaido, Japan; [3]Res. Bldg. D, RIKEN, Hyogo, Japan; [4]Dept. of Physiol. and Cell Biol., Kobe Univ. Sch. of Med., Kobe, Japan

**Abstract:** Social interaction behavior is critical for social animals, including humans. Although there are significant individual differences in social behaviors, reduced sociability is one of the features of autism spectrum disorders (ASDs). It has been reported that inhibitory neuron marker proteins were slightly decreased in autistic brains, suggesting that the excitatory/inhibitory (E/I) balance is important for social behavior. However, the neural mechanisms of inhibitory modulation in social behavior remain unclear. Recently, it has been reported that injuring the insular cortex (IC) causes impairments in empathic responses. In addition, our laboratory previously reported that information on social interaction behavior was encoded in the neural

ensembles named “Social Cells” in IC excitatory neurons of mice [Miura et al., 2020], suggesting that IC is one of the critical brain regions for social behavior. It has been reported that some patients with ASDs showed higher neural activities in IC. From this point of view, we considered that inhibitory interneurons in the IC may modulate social behavior. To address this question, we conducted cell type-specific neural activity recording of IC in mice during social behavior. We examined inhibitory parvalbumin (PV)-positive interneurons or excitatory CaMKII-positive neurons. For interneuron analysis, we injected the AAV-syn-flex-GCaMP6f viral vector into the IC of PV-cre transgenic mice and recorded cellular activities of the PV interneurons by microendoscopic calcium imaging during social interaction in the home cage. As a result, 11.7% of PV interneurons were activated during social interaction, suggesting that social behavior information is encoded in the neural ensembles of PV interneurons in the IC. Furthermore, we analyzed the activities of PV+ neurons during social or object interaction in a linear chamber. In the linear chamber test, 7.0% of PV neurons were activated during the social interaction and 2.6% were activated during object interaction. Interestingly, different cell populations of PV+ neurons were activated in social or object interaction, suggesting that different neural ensembles encode social or object information. For CaMKII-positive neuron analysis, we injected AAV-CaMKII-GCaMP6f into the anterior IC. 19.9% of CaMKII-positive neurons were activated during social interaction and 4.3% were suppressed in the home cage social behavior test. Taken together, our study indicates that both subpopulations of IC pyramidal neurons and inhibitory interneurons encode social information and may modulate social behavior by mutual control among excitatory and inhibitory circuits.

**Disclosures: S. Fujima:** None. **M. Sato:** None. **N. Nakai:** None. **T. Takumi:** None.

**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR051.05/SS3

**Topic:** H.06. Social Cognition

**Title:** Neural mechanism of social reward of cooperation in rats

**Authors: *M. WANG**;
Chinese Acad. of Sci., shanghai, China

**Abstract: Neural mechanism of social reward of cooperation in rat**
Miaoyaoxin Wang[1], Zuo-Ren Wang[1*]*1 Institute of Neuroscience, State Key Laboratory of Neuroscience, CAS Center for Excellence in Brain Science & Intelligence Technology, Chinese Academy of Sciences, Shanghai 200031, China*
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**Abstract:** Cooperation is common in nature and pivotal to the development of human society. Reciprocity is believed to play a significant role in the evolution and maintenance of

cooperation. However, the mechanism of how reciprocity contributes to the evolution and maintenance of cooperation remains poorly understood. To address this gap, we designed an automated reciprocity behavior paradigm modified from a mutualism task previously established by our lab. In our paper, we found that the social experience of reciprocity (being helped or not) could manipulate rats' preference for their helper and non-helper in a three-chamber task. Moreover, we demonstrated that activities of single neurons in the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) in rats differed between social water (received during the cooperation task) and individual water (received during the non-cooperation task). Additionally, by recording the dynamics of dopamine (DA) release with a genetically encoded fluorescent DA sensor using in vivo fiber photometry, we found a higher DA sensor signal in the nucleus accumbens (NAcc) when rats received social rewards compared to individual rewards (equal quantity of water). Based on these results, we hypothesize that the higher DA signal in the NAcc may represent heightened positive feelings that contribute to the evolution and maintenance of cooperation. However, dopamine has two different types of receptors with opposite effects on neurons. Elucidating which type of dopamine receptor receives these dopamine signals in the NAcc is part of our future plan. Manipulation of specific neurons (D1 receptor or D2 receptor) in both the reciprocity task and the manipulation of reciprocity experience could help us understand what kind of information is encoded by dopamine in the NAcc.
**Key words:** Reciprocity, Social behavior,Dopamine,Photometry,NAcc.

**Disclosures: M. wang:** None.

**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR051.06/SS4

**Topic:** H.06. Social Cognition

**Support:** NSF Award #1707408

**Title:** Accelerated social representational drift in the nucleus accumbens in a model of autism

**Authors: *P. ZHAO**, X. CHEN, A. BELLAFARD, D. AHARONI, P. GOLSHANI;
Neurol., UCLA, Los Angeles, CA

**Abstract:** Social interactions are critical for development, survival, and reproduction in almost all animals. Impaired social interaction is one of the core deficits of autism spectrum disorder (ASD). The social motivation theory of autism posits that social interaction may be less rewarding in autism. How the nucleus accumbens (NAc), as a key hub of reward circuitry, encodes social interaction and whether these representations are altered in ASD remain poorly understood. Here we performed calcium imaging using miniaturized microscopes (UCLA Miniscope) and identified NAc ensembles which encode social interactions. At the population level, NAc activity patterns and specifically D1 receptor-expressing medium spiny neuron (D1-

MSN) activity predicted social interaction epochs. NAc-based decoders showed higher performance than decoders trained with medial prefrontal cortex (mPFC) or dorsal hippocampal CA1 (dCA1) activity. Interestingly, there were distinct NAc ensembles active during social interaction and during sucrose consumption, suggesting distinct pathways for different reward modalities. Despite high turnover of NAc neurons modulated by social interaction across days, we found a stable population code for social interaction by performing cross-day decoding. Intriguingly, this stability was impaired in the Cntnap2$^{-/-}$ mouse model of ASD. Therefore, social interactions are preferentially, specifically, and dynamically encoded by NAc neurons and social representations are degraded in Cntnap2$^{-/-}$ autism mouse model. To dissect the neural mechanisms of NAc social representation, we used optogenetics to inhibit the activity of different populations of NAc neurons during social interaction. Surprisingly, inhibition of all neurons in the NAc core increased social interaction time and improved sociability in Cntnap2$^{-/-}$ mice. Selective inhibition of D1- or D2-MSNs had reciprocal effects. Inhibition of D1-MSNs decreased social interaction time while inhibition of D2-MSNs increased social interaction time, suggesting D1- and D2-MSNs drive distinct downstream targets and play opposing roles in motivating social interaction. Cell-type specific modulation of NAc may play a critical role for regulating social interactions in multiple disorders where these interactions are affected.

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**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR051.07/SS5

**Topic:** H.06. Social Cognition

**Support:** NRF Grant 23-BR-02-01

**Title:** The impact of amygdala projection to the medial profrontal cortex pathway on social fear

**Authors: *J. YEO**, S. LEE;
KBRI, Daegu, Korea, Republic of

**Abstract:** It has been reported that the activity of the amygdala is increased in patients with high social fear. The medial prefrontal cortex (mPFC) and basolateral amygdala (BLA) modulate social behavior and fear memory. However, the neural mechanism of the amygdala projecting to the mPFC underlying social fear is unknown. We specifically evoked a high level of social fear in the social fear conditioning (SFC) paradigm, but not in object fear conditioning (OFC). By using whole-cell patch clamp recordings, we found that neuronal excitability was increased only in the SFC group of the mPFC projecting BLA neurons, but not in the OFC group. Halorhodopsin (NpHR)-mediated photoinhibition of the BLA-mPFC pathway attenuates social fear in the conditioned group. These results indicate that the BLA-mPFC pathway is necessary to

evoke the expression of social fear. Our findings suggest that the BLA-mPFC circuit is critical in governing social fear behavior.

**Disclosures:** **J. Yeo:** A. Employment/Salary (full or part-time); KBRI. **S. Lee:** 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.; KBRI.

**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR051.08/SS6

**Topic:** H.06. Social Cognition

**Support:** ARC Grant FT200100843

**Title:** Functional connectivity analyses reveal differences between interaction and observation mode in the macaque visual cortex.

**Authors: *J. TAUBERT**[1], S. JAPEE[2], A. PATTERSON[3], E. BLISS-MOREAU[4];
[1]The Univ. of Queensland, St Lucia, Australia; [2]NIH, NIH, Bethesda, MD; [3]Lab. of Brain and Cognition, The Natl. Inst. of Mental Hlth., Bethesda, MD; [4]UC Davis, UC Davis, Davis, CA

**Abstract:** The dedicated face-selective patch network positioned in the macaque visual cortex is assumed to play a pivotal role in social cognition by processing facial cues. However, how this network operates under more naturalistic, social demands remains poorly understood. Here we used contrast-agent enhanced, high-field (4.7T) functional MRI to measure movie-evoked activity in the visual cortex of three adult rhesus macaques (*Macaca mulatta*). While in the scanner, these animals were shown movies of different social interactions that varied in valence (positive vs. negative), arousal (high vs. low) as well as social distance (interaction vs. observation). While motion sensitive areas such as MT were activated more by movies classified as high arousal (e.g., aggressive fights between conspecifics and mounting behaviors) than movies classified as low arousal (e.g., grooming behaviours), the face-patches, defined using independent localizer data, were activated more by movies classified as direct interactions (e.g., a conspecific directing affective behavior towards the subject) than movies classified as observations (e.g., multiple conspecifics directing their behavior towards each other, and not the subject). Multi-voxel pattern analysis employed at the level of the inferior temporal cortex, defined as the combination of the cytoarchitectonic regions known as TE, TEO, and the Superior Temporal Sulcus, showed that interaction movies evoked a different pattern of activity across voxels than observation movies. We used a psychophysiological interaction (PPI) analysis, seeded on the canonical face- and body- patches, to identify functional connectivity changes across direct and observed social interactions. Taken together, these results reveal that the visual cortex has two modes of operation that support social cognition under different circumstances;

interaction mode is triggered by the subject's direct inclusion in a social interaction, whereas observation mode is triggered by watching third parties interact with each other.

**Disclosures:** **J. Taubert:** None. **S. Japee:** None. **A. Patterson:** None. **E. Bliss-Moreau:** None.

**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

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**Program #/Poster #:** PSTR051.09/SS7

**Topic:** H.06. Social Cognition

**Support:** NIH/NIMH Grant R21MH122798
NSF grant 1942176

**Title:** Contributions of extended frontal association cortex neural circuits to social behaviors in rats

**Authors: *E. CHO**[1], S. MATSUI[2], D. E. MOORMAN[3];
[1]Psychological and Brain Sci., UMASS AMHERST, Amherst, MA; [2]Smith college, Northampton, MA; [3]Psychological and Brain Sci., Univ. of Massachusetts Amherst, Amherst, MA

**Abstract:** The frontal association cortex (FrA) is considered to have important roles in receiving and sending information for cognitive processes including memory formation and working memory. However, the role of FrA in social behavior has not been explored yet. Social interaction refers to either affiliative or aversive behaviors with conspecifics in rodents, which can be measured through observation of social interaction as well as by characterizing appetitive or aversive ultrasonic vocalizations (USVs). In the current studies, we investigated the role of FrA and connected brain regions using circuit mapping, c-Fos activation, and DREADD manipulation. We used adeno-associated virus (AAV) and fluorescent retrobeads to trace anterograde or retrograde neuronal circuits in the male Long-Evans rat brain. We bilaterally injected 500 nl of pAAV8-hSyn-eGFP into the FrA (AP +5.2 ML ±1.8 DV -2.4) and fluorescent retrobeads into either mediodorsal thalamus (MD, AP -3.1 ML ±0.45 DV -5.4) or basolateral amygdala (BLA, AP -2.6 ML ±4.7 DV -8.2). After incubation periods, we tested social behavior and quantifying interaction event bout number and interaction time between a novel same-sex juvenile stimulus rat and the adult experimental rat. We also recorded USVs to analyze communication and affective state during social interaction. Rat brains were obtained 60 minutes after social interaction for immunohistochemical labeling of c-Fos and neuronal circuit tracers. We observed the robust amount of eGFP tagged virus expression in FrA and its axon projection from FrA to dorsal and ventral medial prefrontal cortex (dmPFC, vmPFC), MD and paracentral thalamus, and BLA. Rats showed more affiliative than aversive behaviors as measured by increased affiliative bouts, longer affiliative event duration, and the higher percentage of appetitive (~50 kHz) USV calls relative to aversive behaviors. In alignment with previous

results, we confirmed that that social interaction activated neurons in vmPFC, MD, and BLA through c-Fos immunohistochemistry staining (social interaction group) compared to arena exploration in the absence of social interaction (no-social exploration group). In addition, we also observed that c-Fos expression levels in FrA were decreased in the social interaction group compared to those in the no-social exploration group. Our results suggest that FrA might be a novel brain region regulating social interaction through strong connections with well-characterized social neural hubs, and that further understanding of this brain region will expand our knowledge of the neural circuits underlying social behavior.

**Disclosures: E. Cho:** None. **S. Matsui:** None. **D.E. Moorman:** None.

**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

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**Program #/Poster #:** PSTR051.10/SS8

**Topic:** H.06. Social Cognition

**Support:** NIH Grant DA022340

**Title:** Characterization of simultaneous fiber photometry recordings in anterior cingulate cortex and ventral tegmental area during a pavlovian social outcome paradigm with deeplabcut pose estimation

**Authors: *S. M. RYAN**[1], L. Y. ZHANG[1], A. Y. KIM[1], M. R. ROESCH[2], J. F. CHEER[1]; [1]Neurobio., Univ. of Maryland Sch. of Med. Program In Neurosci., Baltimore, MD; [2]Univ. of Maryland at Col. Park, College Park, MD

**Abstract:** The ability of social animals to modify their behavior based on the experiences of their peers is an important skill in social learning and empathy, which are impaired in psychiatric disorders such as psychopathy and autism spectrum disorder. In this study, we expanded upon prior work to describe the neural mechanisms driving social behaviors related to empathy in rodents. Littermates of C57BL/6J mice were divided into experimental and conspecific subjects. Experimental mice were injected in the anterior cingulate cortex (ACC) and ventral tegmental area (VTA) with a viral vector carrying GCaMP6f and implanted with fiber optic cannulae in the same regions to enable simultaneous fiber photometric recording of localized neuronal activity. Conspecific mice are unsurgerized control mice that were group-housed with their experimental partner. Both experimental and conspecific mice underwent a Pavlovian social outcome paradigm in which an outcome-specific auditory cue and subsequent directional light cue preceded a pseudorandomized outcome. These outcomes were reward, shock, or neutral, and were experienced by the mouse with an active directional light cue. Throughout the session, video of both mice was recorded and synchronized to photometry recordings. Post-hoc posture estimation was conducted using DeepLabCut analysis of video recordings. Using these datasets, we can compare temporal encoding with millisecond precision between the VTA and ACC, as

well as provide behavioral context for distinct patterns of neural activity via synchronized DeepLabCut analysis of stereotyped social behaviors. Early results in well-trained mice indicate that activity in the ACC shows a strong association with all cues and outcomes, supporting prior studies indicating the ACC's role as a signal of attention. VTA activity in well-trained mice shows variation due to outcome type, and minor variations due to social context. Results from mice in early training are being processed; we expect that encoding in the ACC will be affected by social context and outcome type, and VTA activity should encode positive or negative reactions to conspecific reward and shock. These results, coupled with the behavioral context provided by DeepLabCut analysis, should provide a novel perspective on how social context affects encoding in the VTA-ACC circuit.

**Disclosures: S.M. Ryan:** None. **L.Y. Zhang:** None. **A.Y. Kim:** None. **M.R. Roesch:** None. **J.F. Cheer:** None.

**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR051.11/SS9

**Topic:** H.06. Social Cognition

**Support:** NIH R01-NS112518
University of Minnesota MnDRIVE Brain Conditions Initiative

**Title:** A connection from the fastigial nucleus to the supramammillary area and its influence on social behavior in mice.

**Authors: *S. D. HASTINGS**, J. M. WEINER, M. TETZLAFF, E. KROOK-MAGNUSON; Univ. of Minnesota Twin Cities, Minneapolis, MN

**Abstract:** Despite the lack of a direct monosynaptic connection, manipulation of the cerebellum can modulate activity of the hippocampus. We hypothesize that the supramammillary area of the hypothalamus (SuM) is a potential intermediary between the cerebellum and the hippocampus, as the SuM has been shown to receive projections from the cerebellar fastigial nucleus (FN) and is known to innervate hippocampal CA2 and the dentate gyrus (DG). Connections from the SuM to the hippocampus are believed to be important for signaling social (SuM→CA2) and spatial (SuM→DG) novelty. In contrast, the connection from the FN to the SuM has not been previously explored. With a transsynaptic anterograde adeno-associated virus (AAV) strategy in mice (n=4) we observe that SuM cells that receive synaptic input from the FN subsequently project to hippocampal CA2. To examine the specific function of FN→SuM signaling we use a dual-virus cre-dependent AAV optogenetic strategy. Our preliminary results suggest that specific optogenetic stimulation of FN→SuM neurons can modulate hippocampal local field potentials (n=2). Using this same viral paradigm, we are testing the effects of FN→SuM optogenetic stimulation on social behavior in mice in an open arena social task. Our early results indicate a

trend that mice receiving optogenetic stimulation of FN→SuM neurons (n=5) have diminished social recognition behavior compared to opsin-negative controls (n=8). Given our preliminary results that *in vivo* optogenetic stimulation of FN→SuM neurons during behavior results in an alteration of social recognition processing and our observations with AAV1 experiments, suggesting a FN→SuM→hippocampal CA2 pathway, we hypothesize that FN→SuM neurons are involved in hippocampal dependent social processing. Ongoing and future work will further characterize the functional connectivity of FN→SuM neurons and their involvement in social and spatial behaviors.

**Disclosures: S.D. Hastings:** None. **J.M. Weiner:** None. **M. Tetzlaff:** None. **E. Krook-Magnuson:** None.

**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

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**Topic:** H.06. Social Cognition

**Support:** NIH F31HD108043
NIH T32NS115753
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NIH R01NS117597

**Title:** Neural circuits underlying social touch deficits in mouse models of autism.

**Authors: *T. CHARI**, A. HERNANDEZ, C. PORTERA-CAILLIAU;
Univ. of California - Los Angeles, Los Angeles, CA

**Abstract:** Social touch, an important aspect of social interaction and communication, is essential to kinship across animals and humans. Individuals with autism spectrum disorders (ASD) are apprehensive to social touch, but the underlying circuit mechanisms have not been thoroughly investigated in animal models, in part due to the lack of appropriate assays. We designed a novel head-fixed assay for social touch in mice, in which the experimenter has complete control to elicit highly stereotyped bouts of social touch between two mice. We determine the number, duration, context, and type of social touch interactions while monitoring with high frame rate cameras an array of complex behavioral responses. We focused on social touch to the face because of its high translational relevance. We validated this assay in two different models of ASD, the *Fmr1* knockout model of Fragile X Syndrome and maternal immune activation mice. We observed increased avoidance, hyperarousal, and more aversive facial expressions to social touch, but not to object touch, in both autism models compared to controls. Because this new social touch assay for head-fixed mice can be used to record neural activity during repeated bouts of social touch, we then used Neuropixels probes to chronically record single-unit activity of behaviorally relevant neuronal populations in barrel cortex (S1BF), dorsal striatum and

basolateral amygdala (BLA), all of which showed high cFos expression during social touch (in TRAP2 mice). We identified individual neurons in all three regions whose activity is modulated by social touch and that show context preference for social versus object touch. Furthermore, we found a higher proportion of touch-responsive cells and significantly reduced adaptation to repetitive bouts of social touch in the activity of touch-responsive cells of Fmr1 knockout mice in S1BF and BLA. We will also present data that correlates neuronal activity in these brain regions to the maladaptive behaviors to social touch. Thus, our novel assay for mice shows a strong translational potential for investigating behavioral responses to social touch in autism.

**Disclosures: T. Chari:** None. **A. Hernandez:** None. **C. Portera-Cailliau:** None.

**Poster**

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**Program #/Poster #:** PSTR051.13/SS11

**Topic:** H.06. Social Cognition

**Support:** LF grant R310-2018-3611

**Title:** Feed-forward inhibition of ventral CA1 by endopiriform nucleus contributes to social discrimination

**Authors:** N. YAMAWAKI[1], H. LOGIN[1], S. Ø. FELD-JAKOBSEN[1], B. M. MOLNAR[1], M. S. KIRKEGAARD[1], M. MOLTESEN[1], J. M. RADULOVIC[2,1], ***A. TANIMURA**[1];
[1]Biomedicine, Aarhus Univ., Aarhus, Denmark; [2]Albert Einstein Col. of Med., Albert Einstein Col. of Med., the Bronx, NY

**Abstract:** The ventral hippocampus, in particular its CA1 subfield (vCA1), is implicated in social discrimination (Meira et al., Nat Communi 2018, Okuyama et al., Science 2016). In many mammals, this memory-guided behavior relies on social odor (Sanchez-Andrade and Kendrik., Behav Brain Res 2009). The social odor information is thought to be integrated by vCA1 via a circuit encompassing the lateral entorhinal cortex and dorsal CA2 (Leitner et al,. Nat Neurosci 2016, Lopez-Rojas et al., Neuron 2022). However, there is some evidence indicating that vCA1 receives axons from the endopiriform nucleus (EN), which anatomically sits at the intersection between vCA1 and the olfactory system thus, may contribute to social/odor discrimination processing in vCA1. Nevertheless, we know very little about its circuit organization and function. By combining viral circuit tracing, *ex vivo* electrophysiology, optogenetics, chemogenetics, and behavioral analysis on adult mice (both sex), we found axons from EN project to, and preferentially connect to interneurons in vCA1 in a layer-specific manner. Photostimulation of EN axons evoked little excitatory postsynaptic current (EPSC) but the robust inhibitory postsynaptic current (IPSC) on vCA1 pyramidal neurons (22.26 pA ± 29.25 vs 376.76 ± 310 28 pA (mean ± SD); $n = 22$, $p < 0.001$ (signed rank test)), suggesting EN axons primarily inhibit pyramidal neurons by recruiting local interneurons in vCA1. Monosynaptic rabies tracing

revealed that the vCA1-projecting neurons in EN mainly receive input from the piriform cortex known to process odor information. Chemogenetic inhibition of vCA1-projecting neurons in EN impaired social discrimination but not sociability. These findings thus suggest that the EN to vCA1 circuit contributes to social discrimination processing via feed-forward inhibition of vCA1 pyramidal neurons.

**Disclosures:** **N. Yamawaki:** None. **H. Login:** None. **S.Ø. Feld-Jakobsen:** None. **B.M. Molnar:** None. **M.S. Kirkegaard:** None. **M. Moltesen:** None. **J.M. Radulovic:** None. **A. Tanimura:** None.

**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

**Location:** WCC Halls A-C

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**Topic:** H.06. Social Cognition

**Support:** HFSP fellowship LT0055/2022-L

**Title:** Cortical circuit for social interaction

**Authors: *N. DOLENSEK**, D. TSAO;
UC Berkeley, Berkeley, CA

**Abstract:** Social interaction affects almost every aspect of our lives and relies on rapid integration of social cues like gaze direction and facial expression to produce appropriate social behavior. However, brain circuits underlying this extremely complex function are not currently well understood. Macaques, like humans, exhibit complex social behaviors, and possess highly similar brains, rendering them an ideal model system for investigating the neural basis of social interaction. Here, we employ a multimodal approach to gain a mechanistic understanding of social interaction, combining whole-brain functional magnetic resonance imaging (fMRI), electrical microstimulation, and high-density electrophysiology using Neuropixels probes in macaques. Our approach incorporates naturalistic social interaction stimuli within a virtual reality (VR) environment and using closed-loop interaction with a virtual avatar, simulates real-world social experiences. Through this innovative framework, we identify a comprehensive network of cortical brain regions encompassing perception, cognition, emotion, and behavioral domains, that perform integration of social cues and enable bidirectional social interaction.

**Disclosures:** **N. Dolensek:** None. **D. Tsao:** None.

**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

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**Topic:** H.06. Social Cognition

**Support:** IBS-R001-D2

**Title:** Dynamic and stable hippocampal representations of social identity and reward expectation support associative social memory in male mice

**Authors: E. KONG**[1], K.-H. LEE[1], J. DO[1,2], *D. LEE[1];
[1]Ctr. for Cognition and Sociality, Inst. for Basic Sci., Daejeon, Korea, Republic of; [2]Dept. of Biol. Sci., Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of

**Abstract:** Within a social group, animals engage in frequent and repetitive interactions with one another. During these interactions, animals recognize others as unique individuals, retrieve and update the value information assigned to the individual. These abilities are essential for establishing and maintaining social relationships in cohesive social groups. However, the neural mechanism underlying association between social identity and reward value remain poorly understood. To identify neural activities related to individual identity as well as associated reward values in the dorsal CA1, we developed Go-NoGo social discrimination paradigms that required subject mice to distinguish between familiar mice based on their individually unique characteristics and associate them with reward availability. Through a brief nose-to-nose investigation, mice could discriminate between conspecific mice associated with rewards and those associated with no rewards, and this ability was found to depend on the dorsal hippocampus. Notably, the social memory established during the task remained stable for a week, even though the subject mice were single-housed. Two-photon calcium imaging revealed that dorsal CA1 hippocampal neurons represented reward expectation during social, but not non-social tasks, and these activities were maintained over days regardless of the identity of the associated mouse. Furthermore, hippocampal neurons accurately discriminated between familiar mice either in the reward or no-reward category at both the single-cell and population levels. We also demonstrated that an ever-changing subset of dorsal CA1 neurons, which allow a certain degree of overlap in mouse-selective neurons, contributes to the stable encoding of individual-specific information over days. Taken together, our findings suggest that the neuronal activities in CA1 provide possible neural substrates for associative social memory.

**Disclosures: E. Kong:** None. **K. Lee:** None. **J. Do:** None. **D. Lee:** None.

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**Topic:** H.06. Social Cognition

**Support:** NSERC Grant RGPIN-2018-04699

**Title:** Estrogen rapidly facilitates social (but not nonsocial) short term memory in the medial Prefrontal Cortex and do not increase extracellular oxytocin

**Authors:** *S. PENG, O. KACHMARCHUK, M. WILSON, Y. B. OREN, **E. CHOLERIS**; Psychology, Univ. of Guelph, Guelph, ON, Canada

**Abstract:** The estrogen 17β-estradiol (E2), rapidly facilitates short-term memories of Social Recognition (SR) and the Social Transmission of Food Preferences (STFP) in ovariectomized (OVX) mice. E2 rapidly facilitates SR when infused into the medial amygdala (MeA), and this rapid facilitation depends upon the activity of oxytocin (OT) receptors (OTR) in the MeA. In addition, infusion of E2 into the Paraventricular nucleus of (PVN) the hypothalamus where the largest population of OT neurons is found in the mouse brain, facilitated SR and increased extracellular oxytocin in the MeA. Medial Prefrontal Cortex (mPFC) also has high estrogen receptors (ERs) and OT receptors expression and receives OT neuron projections from the PVN. Therefore, we examined whether E2 also rapidly facilitated SR in the mPFC, which ERs mediated the rapid SR facilitation if present, and whether E2 in the mPFC rapidly facilitated social learning in the STFP, as well as non-social types of short-term memory (Object Recognition (OR) and Object Placement (OP)). We additionally assessed whether E2 infusions induced an increase in mPFC extracellular OT level. Our results showed that E2 infused into the mPFC of OVX mice rapidly facilitated SR and STFP short-term memory, but not non-social short-term memory in the OR and OP tasks. We also found that the facilitation of SR was replicated by administration of agonists for each of the three main ERs, ERα, ERβ, and G protein-coupled ER 1 (GPER1). However, a microdialysis study showed that E2 in the mPFC did not rapidly increase extracellular OT level. Altogether, this study reveals estrogens' role on rapid facilitation of social, but not nonsocial cognition in mPFC of female mice and suggests that this rapid facilitation does not require an increase in extracellular OT, thus requiring further investigation of alternative mechanisms.

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**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

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**Program #/Poster #:** PSTR051.17/SS15

**Topic:** H.06. Social Cognition

**Support:** Grant Agency of the Czech Republic Grant #19-07983Y

**Title:** Selective targeting of cortical beta2*-containing nicotinic acetylcholine receptors shapes social behavior

**Authors: *A. ABBONDANZA**[1,2], C. GOTTI[3], S. DUMAS[4], V. BERNARD[2], H. JANICKOVA[1];
[1]Neurochemistry, Inst. of Physiol. of the Czech Acad. of Sci., Prague, Czech Republic; [2]Neurosci. Paris Seine, Sorbonne Université, CNRS UMR 8246, Paris, France; [3]CNR, Inst. di Neurosci., Milano, Italy; [4]Oramacell, Paris, France

**Abstract:** Cholinergic receptors are differentially distributed across the cortex and the activation of nicotinic acetylcholine receptors (nAChRs), located on principal neurons and GABAergic interneurons (GABAINs), modulates synaptic plasticity and behavior. Despite their undisputed importance, functional consequences of selective activation or inhibition of nAChRs expressed by the different types of cortical neurons is not well understood. We used two different methods, Cre-loxP and CRISPR/Cas9-based approach, to delete the most abundant beta2 nicotinic subunit in the mouse prefrontal cortex (PFC). First, we used fluorescent in situ hybridization to characterize the expression of beta2*nAChRs in different types of cortical neurons. Then, we prepared different cohorts for behavioral testing. We injected in the PFC a first group of beta2-flox/flox mice with AAV-Cre virus. Alternatively, we crossed a mouse line expressing Cas9-GFP in a Cre-dependent manner with NPY-Cre or Htr3a-Cre: litters were injected with an AAV carrying sgRNA targeting CHRNB2 (gene coding for beta2 nicotinic subunit). The CRISPR-induced mutations in CHRNB2 gene in the PFC of NPY- and Htr3a- expressing neurons led to changes in sociability, while the broader Cre-loxP-mediated deletion of beta2-nAChRs had little effect on the behavioral phenotype. Finally, we performed binding assays to compare the efficiency of the two methods in deleting nAChRs. In conclusion, selective deletion of nAChRs in specific neuronal types can be achieved by CRISPR/Cas9-based approach and the effects on behavior depend on the type of the targeted neurons.

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**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

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**Program #/Poster #:** PSTR051.18/SS16

**Topic:** H.06. Social Cognition

**Support:** NIH Grant R01 DC019653

**Title:** Exploring natural social interactions in humans at the single neuronal level

**Authors: *I. CAPRARA**[1,3], E. MAYER[4], A. O. BOTTINGER[4], J. CAI[1,3], Y. KFIR[1], A. C. PAULK[1,3], B. MASH[4], M. JAMALI[1,3], S. YEE[4], D. J. KELLAR[1,3], S. S. CASH[2,3], Z. WILLIAMS[1,3];
[1]Neurosurg., [2]Neurol., MGH, Boston, MA; [3]Harvard Med. Sch., Boston, MA; [4]Northeastern Univ., Boston, MA

**Abstract:** Human social interactions are complex and depend on our ability to communicate effectively with others. These verbal interactions are dynamic and can vary broadly in content or theme; together reflecting some of the core constructs of human social behavior. Understanding the basic cellular processes that underlie natural social communication in humans, however, has remained a significant challenge. Here, we used a rare opportunity to perform semi-chronic recordings from frontotemporal neurons in participants engaged in natural dialogue as well as linguistic tools and speech tracking approaches to discover detailed cellular representations of their social interactions. By mapping their activities across hundreds of interaction events, we find neurons that reflected the social agency, emotionality, clout, allure, and tone and their real-time dynamics. We show how distinct neurons represented the agency of interaction and how they transitioned across agents. We also show how their activity patterns reliably predicted not only the types of interaction but also the other's social agent's upcoming response. Together, these findings begin to shed light on some of the basic cellular building blocks that underlie natural social communication in humans and provide a reference point from which to better understand social behavioral and communication disorders at a neuronal level.

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**Program #/Poster #:** PSTR051.19/SS17

**Topic:** H.06. Social Cognition

**Support:** NSF Grant 1937971

**Title:** Sensory encoding of emotion conveyed by the face and visual context

**Authors: *K. M. SODERBERG**[1], G. JANG[2], P. A. KRAGEL[1];
[1]Psychology, [2]Neurosci., Emory Univ., Atlanta, GA

**Abstract:** Humans are constantly confronted with sensory signals that have emotional meaning, which they rapidly detect and interpret. Facial expressions are particularly important signifiers of emotion, and are thought to be processed by a network of brain regions including amygdala and posterior superior temporal sulcus (pSTS). Previous work suggests that pSTS integrates dynamic facial movements and maps this information to emotional meaning, whereas amygdala tracks salient information conveyed by faces. However, less is known about what computations these regions perform, and whether expression-specific representations are present in both regions. To probe the brain representations of visual emotion signals, we used artificial neural networks (ANNs) optimized for two different tasks: recognizing emotions from faces (Toisoul et al., 2021) and classifying the emotion schema from visual scenes (Kragel et al., 2019). We used these

ANNs to process the movie *500 Days of Summer* and extract features relevant to facial expressions and the broader visual context, respectively. Then, using fMRI data from subjects viewing the movie (Aliko et al., 2020), we fit encoding models using multivariate regression to map these features to activity in the amygdala and pSTS. We predicted that activity in later layers of the facial expression recognition model would meaningfully explain activity in the pSTS and not the amygdala, with the opposite pattern for the emotion schema model. We found partial support for this hypothesis: only the emotion schema model significantly explained amygdala activity, whereas both the facial expression and schema models significantly explained pSTS activity. This effect was present using activity in late, but not intermediate layers of the ANNs ($F_{2,38} = 7.42$, $p = .005$, partial $\eta^2 = .281$). To determine whether each of these explained unique variance in pSTS activity, we tested a model that combined features from both ANNs and found that it explained more variance than either model alone. This suggests that the pSTS contains representations of facial expressions and the broader visual context. The amygdala, on the other hand, may not operate on categorical representations of facial expressions, such as 'fear', 'anger', and 'joy', but encodes emotional significance from visual information more broadly. This work has implications for the role of these regions in face processing and sensory encoding of emotion in more naturalistic contexts. Although ANNs are far from veridical reproductions of brain mechanisms, they can illuminate what information is represented in a given brain region, allowing for a more fine-grained understanding of neural processing.

**Disclosures: K.M. Soderberg:** None. **G. Jang:** None. **P.A. Kragel:** None.

**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR051.20/SS18

**Topic:** H.06. Social Cognition

**Support:** R01MH130862

**Title:** Chd7 deficiency in postmitotic ACC neurons reduces innate anxiety and enhances social behaviors in mice

**Authors: *E. M. DEW**[1], S. SAGGU[2], K. JIAO[3], Q. WANG[4];
[1]Augusta Univ. Neurosci. Grad. Program, Augusta, GA; [2]Augusta Univ., Augusta Univ., Augusta, GA; [3]1462 Laney Walker Blvd. CA4098, Augusta, GA 30912, Med. Col. of Georgia at Augusta Univ., Augusta, GA; [4]Med. Col. of Georgia, Med. Col. of Georgia, Augusta, GA

**Abstract: *Chd7* deficiency in postmitotic ACC neurons reduces innate anxiety and enhances social behaviors in mice**
Emily Dew, Shalini Saggu, Kai Jiao, Qin Wang
CHD7 is a SNF2-like ATP-dependent chromatin remodeling factor, and heterozygous *CHD7* loss of function mutations in humans result in CHARGE syndrome (coloboma, heart defects,

atresia choanae, growth retardation, genital abnormalities, and ear abnormalities), which also presents neurological deficits. CHD7 facilitates proliferation, quiescence, and migration of neural stem cells and is necessary for migration of neural crest cells. However, its expression and function in adult postmitotic neurons remain largely unknown. We have identified that *Chd7* expression is enriched in excitatory neurons in the anterior cingulate cortex (ACC) in adult mice. In order to study the role of *Chd7* in postmitotic ACC neurons, we employed *Chd7*$^{loxp/loxp}$ mice and introduced Cre expression in the ACC through an adeno-associated viral system. ACC deficiency of *Chd7* led to decreased anxiety-like behavior in open field, elevated zero maze, and light/dark tests. These phenotypes were observed only in male, but not in female, mice, indicating sexual dimorphism of CHD7 function. Furthermore, the male *Chd7* conditional knockout mice showed increased sociability in both a three-chamber social interaction test and a free social interaction test. Our study suggests that CHD7 in postmitotic ACC neurons is important in regulating both anxiety-like and social behaviors.

**Disclosures: E.M. Dew:** None. **S. Saggu:** None. **K. Jiao:** None. **Q. Wang:** None.

**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR051.21/SS19

**Topic:** H.06. Social Cognition

**Title:** A REINFORCEMENT CIRCUIT FOR SOCIAL DECISION MAKING

**Authors: *E. DEMIR**;
Anat., Southern Illinois University, Sch. of Med., Carbondale, IL

**Abstract:** Few decisions are as important to an animal as choosing when and with who to mate, while maintaining the metabolic needs, referred as “resource-allocation problem”. These mate decisions contribute to both the fitness of individuals and the emergency of the evolutionary diversity, yet we know little about their neurobehavioral mechanisms. In our recent published work, we defined a genetically determined circuit—extending from the accessory olfactory bulb to the posterior medial amygdala—that reinforces female mouse behaviors to promote mate selection[1]. We further characterized that this topographically segregated reward circuit in the medial amygdala (MeA) expresses nNOS, neuronal nitric oxide synthase. Here, I present further evidence regarding this sexually mono-morphic reward circuit, MeA-nNOS, and how it may contribute to mate selection also in male mice. To test whether MeA-nNOS neurons are required for the reinforcement of social interactions with females, we first developed a social-preference based decision task that establishes a direct trade-off between social and non-social rewards. This trade-off task uses the fundamental premise that time spent in social interaction is directly proportional to social interest, allowing us to measure the value of each social cue relative to the value of a common reference (the water reward). In this decision task, we simply quantify the temporal trade-off between social and water rewards- by contrasting time spent in a social

interaction with a delay in receiving the water reward. We show that male mice form a robust preference of female cues with a rank order that remains stable over many months, suggesting that animals maintain these social-value representations over long periods. We demonstrate that the preference for a specific social cue can be adjusted by manipulating the amount of water reward that an animal receives, establishing a direct trade-off between social and non-social rewards, and that the time spent with a cue is related to social preference as well as the magnitude of the water reward. Hence, male mice impose a relative value on every social interaction. Lastly, we show that silencing of MeA-nNOS during this reward task, suppresses social interest towards social cues. Thus, the MeA-nNOS integrates sensory information with internal reproductive states to reinforce social behaviors that optimize mate seeking in both genders. In future studies, we plan to characterize the projections of these MeA-nNOS to prefrontal brain regions to further study the neuronal instantiation of relative value in social decision-making. References: 1. Demir E, *et. al.*Nature. 2020 Feb;578(7793):137-141

**Disclosures: E. Demir:** None.

**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

**Location:** WCC Halls A-C

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**Topic:** H.06. Social Cognition

**Support:** NIH Grant P50MH100023
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Narsad YI Grant (2017)

**Title:** Natural variation in prairie vole oxytocin receptor signaling causes widespread changes in neural transcription

**Authors: *A. J. BOENDER**, Z. V. JOHNSON, K. HORIE, H. WALUM, L. J. YOUNG; Emory Univ., ATLANTA, GA

**Abstract:** Natural variation in brain oxytocin receptor (*Oxtr*) expression contributes to diversity in social behaviors. In socially monogamous prairie voles (*Microtus ochrogaster*), variation in *Oxtr* expression in nucleus accumbens (NAc) is associated with variation in pair bonding, alloparental behavior and resilience to neonatal social neglect. Previously, we found a set of nine single nucleotide polymorphisms in and near the *Oxtr* gene that largely explain individual variation in *Oxtr* expression, specifically in NAc ($r^2$>0.7). Here, we apply bulk ATAC and RNA-seq, and single nucleus RNA-seq (snRNA-seq) on two vole genotypes that produce low or high NAc OXTR to investigate how variation in NAc OXTR expression affects brain transcription. We confirm differential expression (DE) of NAc *Oxtr* and reveal widespread neural transcriptional changes. We find an enrichment for DE genes (DEGs) and open regions on the

*Oxtr* chromosome ($P_{adj}$<0.1). The *Oxtr* chromosome harbors several C-type lectin receptors (CLRs) in a genomic region known as the natural killer gene complex (NKC). CLRs are involved in self-recognition and cell adhesion; and positioned to regulate the shaping of neural circuitries. Specifically, we find two CLRs to be strongly DE: *Clec12a* and *Klrb1a* ($P_{adj}$<0.01). Using snRNA-seq, we confirm DE of *Oxtr, Clec12a* and *Klrb1a* ($P_{adj}$<0.01). We find that *Clec12a* is specifically expressed in microglia (P<0.001), and that *Klr1b1a* expression strongly localizes to cell types that express *Oxtr* (P<0.01). Interestingly, many DEGs are present in astrocytes and oligodendrocytes, cell types that express little or no *Oxtr*. These findings suggest strong *trans* effects of genotype on neural transcription. To understand how variation in OXTR density leads to altered *Clr* expression, we used *Oxtr* knock-out (KO) prairie voles produced on a high OXTR genetic background. Again, we confirm DE of *Oxtr, Clec12a* and *Klrb1a* ($P_{adj}$<0.01). However, expression of *Clec12a* and *Klrb1a* in *Oxtr* KO animals ($P_{adj}$<0.01) mirrors low OXTR genotypes, demonstrating that variation in OXTR signaling - not genetic variation *per se* - drives *Clr* DE. Considering the emerging role of immune pathways in neurodevelopmental processes, for example through microglial pruning of synapses, we hypothesize that variation in OXTR signaling during development influences NKC activity and profoundly impacts neural circuit functioning, thus providing a potential mechanism by which early nurturing and social experience can shape adult social behaviors. Here, we present the prairie vole as a unique model to investigate how immune pathways shape neurodevelopment, and the role OXTR signaling plays herein.

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**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR051.23/SS21

**Topic:** H.06. Social Cognition

**Support:** MH-11856304

**Title:** Male Mecp2 knockout mice do not form stable social hierarchies: a consequence of impaired social memory due to lack of neuronal synchrony in the mPFC?

**Authors: *C. ACEVEDO-TRIANA**[1], L. POZZO-MILLER[2];
[1]Univ. of Alabama At Birmingham, Birmingham, AL; [2]Neurobio., Univ. Alabama-Birmingham, Birmingham, AL

**Abstract:** The activity of mouse mPFC neurons is correlated with the interaction with conspecifics and is thought to encode social memories used to establish hierarchical social rankings. Atypical social behaviors are prevalent in neurodevelopmental disorders, and a mouse model of Rett syndrome shows impaired social memory caused by heightened activity of the

monosynaptic projection from the ventral hippocampus to the mPFC. We performed the classical 'tube' test over 6 consecutive days to establish the social hierarchy within groups of 3 age-matched male mice of the same genotype. This assay revealed that *Mecp2* KO mice failed to form stable social ranks, displaying fewer dominant behaviors inside the tube than WT mice. We followed the 'tube' test with a novel 'warm' spot test, where the same 3 age-matched mice of each genotype compete to stand on a single warm spot in a cage with a cooled floor. As expected, the 'dominant' WT mouse occupied the 'warm' spot far longer than the other 2 mice ('intermediate' and 'submissive'), while *Mecp2* KO mice equally shared the 'warm' spot regardless of their social rank, showing fewer dominant behaviors than WT mice. *In vivo* $Ca^{2+}$ imaging with head-mounted miniscopes to follow neuronal activity in unrestricted mice poses a significant challenge to study *Mecp2* KO mice because they begin to have neurological impairments around P50. To overcome this, we performed a single surgery to inject AAVs expressing CaMKII-driven GCaMP6 and implant a GRIN lens in the mPFC of WT mice at P25. After 2 weeks, WT mice displayed stable social ranks in the 'tube' and 'warm spot' tests, indicating that GRIN lens implantation in one hemisphere's mPFC did not affect this social behavior. *In vivo* $Ca^{2+}$ imaging from pyramidal neurons in the prelimbic mPFC confirmed the presence of social-ON and social-OFF cells, i.e., neurons that increase and decrease activity during social interactions, respectively. mPFC pyramidal neurons in *Mecp2* KO mice showed fewer and smaller $Ca^{2+}$ transients during baseline, as well as during social interactions in the 'warm spot' test. The activity of social-ON and social-OFF neurons in *Mecp2* KO mice seems to be less synchronous than in WT mice. To further reduce the number of surgeries and their duration, we tested pre-coating the GRIN lenses with a mixture of jGCaMP-encoding AAV and silk fibroin. Preliminary results in WT mice show that the silk-coating yield comparable numbers of jGCaMP-expressing neurons without affecting the optical performance of GRIN lenses, assessed by raw jGCaMP intensity and the amplitude and kinetics of its $Ca^{2+}$-dependent dF/F transients.

**Disclosures: C. Acevedo-Triana:** None. **L. Pozzo-Miller:** None.

**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR051.24/SS22

**Topic:** H.06. Social Cognition

**Support:** SFARI Bridge to Independence
NIH K08 NS105938

**Title:** Shank3-deficiency drives abnormal recruitment of a heterogeneous social ensemble

**Authors: *H. WALKER**[1], N. A. FROST[2];
[2]Dept. of Neurol., [1]Univ. of Utah, Salt Lake City, UT

**Abstract:** The coordinated activity of heterogeneous cell types across multiple brain regions including the medial prefrontal cortex (mPFC) underlies the representation of salient information during social behavior. SHANK3 is strongly associated with autism spectrum disorders (ASD) and mutation of the protein in mice and humans results in abnormal social interactions. Mice modeling mutations in SHANK3 show cortical hyperexcitability and elevated excitation; how these changes in cellular and synaptic properties affect the representation of social interaction is not well understood. We have previously shown that mice lacking SHANK3 have pathologically elevated activity of prefrontal neurons during home cage exploration and social interaction (Frost, 2021), however the specific contributions of different cell types to this altered activity are not known. We therefore sought to understand how different populations of cells are recruited to ensembles underlying social behavior, and how this composition may be altered in mice lacking SHANK3. Following social interaction, we isolated nuclei from the mPFC and cerebellum from a total of 247,779 cells from 14 WT and 4 KO mice in actinomycin-D to prevent artificial transcriptomic perturbations (Wu, 2017). We then utilized a transcriptomic approach to identify heterogeneous cell types within the mPFC and cerebellum, and then identify cells expressing immediate-early genes (IEGs) as a marker of activity during social interaction. Examination of IEG+ cells from heterogeneous clusters revealed that social interaction resulted in varied recruitment across heterogeneous excitatory and inhibitory neuron populations within the mPFC. Social interaction resulted in the activation of partially overlapping IEGs within heterogeneous cell types in the mPFC and cerebellum at both 10 minutes and 35 minutes after interaction. Finally, in mice lacking Shank3, we observed significantly increased recruitment of layer 2/3 excitatory neurons within the mPFC, consistent with increased excitability of these neurons (Ali, 2021; Yoo, 2019). Taken together, these data suggest that information salient to social interactions is represented by a heterogeneous ensemble of neurons, and composition of this ensemble is altered in mice lacking SHANK3.

**Disclosures: H. Walker:** None. **N.A. Frost:** None.

**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR051.25/SS23

**Topic:** H.06. Social Cognition

**Support:** CONACYT 001805

**Title:** Intranasal oxytocin mediated neural modulation and emotional appraisal during a social cognition task in men and women.

**Authors: *L. CRUZ ZAVALETA**, T. CIBRIAN LLANDERAL, S. ZAMORA LUGO, J. RODRIGUEZ LANDA;
Neuroethology, Univ. Veracruzana, Xalapa, Mexico

**Abstract:** Oxytocin has been the subject of numerous investigations in human social behavior. Its intranasal administration (OXT IN) is able to modify core social behaviors, but has faced obstacles due to lack of research replication, reliable methodological development and transparent experimental practices.The aim of this study was to identify the determinants of performance on different tests of emotional recognition and cognitive and affective empathy based on social cognition and to evaluate the effect of OXT IN in neurotypical subjects. It is a comparative, double-blind, cross-sectional, quantitative, placebo-controlled study. The Interpersonal Reactivity Index (IRI) and the Reading the Mind Through Eyes Test (RMET) were used as assessment instruments.Seventy subjects participated in three groups: oxytocin (OXT IN), placebo (PLB) and control (CTL). A dose of 24 IU of oxytocin or placebo was administered intranasally, followed by cognitive testing after 40 minutes. Results were analyzed with Kruskall Wallis and Wilcoxon tests, where women scored higher on empathic concern (Mdn=26; Range=6) compared to men (Mdn=22.5; Range=6.5) ($W=4851.5$, $p<0.05$, g Hedges=0.612). In addition, the severe anxiety group had more hits than the normal, mild and moderate anxiety groups on the fantasy ($H(3)=27.40$, $p<0.001$), empathic concern ($H(3)=17.44$, $p<0.001$) and personal distress ($H(3)=19.48$, $p<0.001$) subscales.No evidence was found in this study to support previous research, however, it opens possibilities to understand the mechanisms involved in empathy and interpersonal trust, and also highlights the importance of receiving psychological or psychiatric care to improve empathic concern, reduce personal distress, prioritize the other and remain calm in adverse situations.

**Disclosures: L. Cruz Zavaleta:** None. **T. Cibrian Llanderal:** None. **S. Zamora Lugo:** None. **J. Rodriguez Landa:** None.

**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR051.26/SS24

**Topic:** H.06. Social Cognition

**Support:** NIH Z01 ES100221

**Title:** Contrasting roles of perineuronal nets surrounding CA2 pyramidal cells and parvalbumin-expressing interneurons

**Authors: *G. M. ALEXANDER**[1], S. S. MOY[2], S. M. DUDEK[3];
[1]Natl. Inst. of Envrn. Hlth. Sci., Durham, NC; [2]Univ. of North Carolina at Chapel Hill Sch. of Med., Chapel Hill, NC; [3]Neurobio. Lab., Natl. Inst. of Envrn. Hlth. Sciences, Researc, Research Triangle Park, NC

**Abstract:** Perineuronal nets (PNNs) are a specialized extracellular matrix comprised of chondroitin sulfate proteoglycans (CSPGs) that encase select populations of neurons, including parvalbumin (PV)-expressing interneurons and hippocampal CA2 pyramidal neurons. CA2

neurons are unique among hippocampal subfields; in addition to having PNNs, they also lack typical long term potentiation (LTP). Yet, in slices, LTP can be enabled in CA2 upon enzymatic degradation of PNNs with chondroitinase (ChABC) (Carstens et al., 2016). Others have reported impaired social memory, which is dependent on CA2, after direct hippocampal injection of ChABC in mice (Cope et al, 2022). Although these findings implicate PNNs in regulating synaptic plasticity and social behavior, it is unknown whether the effects are due to PNNs on CA2 pyramidal neurons or those on PV cells. To overcome this limitation, we developed a cre-dependent conditional knockout (cKO) mouse strain (i.e., 'floxed') for the primary CSPG of PNNs, aggrecan (ACAN). Floxed ACAN mice bred with either Amigo2-cre mice, which express cre in CA2 pyramidal cells, or PV-cre mice, which express cre in PV interneurons resulted in selective KO of PNNs: Amigo2-cre; ACAN cKOs (CA2 ACAN KOs) lacked PNN staining in CA2 but retained PNN staining on PV cells. Conversely, PV-cre; ACAN cKOs (PV ACAN KOs) lacked PNN staining on PV cells but retained PNN staining in CA2. We assayed several behaviors in these two strains, including preference for social novelty and response to a chemoconvulsant, to determine the behavioral role of PNNs on each cell type independently. In the three-chamber social task, we found that both control and PV ACAN KO animals showed the typical preference for social novelty, but CA2 ACAN KOs did not show this preference. Both CA2 and PV cells are implicated in seizure activity and PNNs are dysregulated in models of epilepsy, so we asked whether response to a chemoconvulsant would be differentially affected in the two ACAN KO strains. Mice were injected with kainic acid (5 mg/kg, ip) every 30 min until they reached status epilepticus (SE) as a means of measuring seizure susceptibility and subsequent severity. CA2 ACAN KOs did not differ from controls in the number of KA injections required to reach SE. However, once mice reached SE, CA2 ACAN KOs were more likely than controls to die during SE, suggesting increased seizure escalation and severity in mice lacking PNNs in CA2. In contrast, PV ACAN KOs required more KA injections than controls to reach SE, suggesting an increased seizure threshold for mice lacking PNNs on PV cells. These findings support a role for CA2 PNNs in social memory and both CA2 and PV PNNs in regulation of neuronal excitability.

**Disclosures:** **G.M. Alexander:** None. **S.S. Moy:** None. **S.M. Dudek:** None.

**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR051.27/SS25

**Topic:** H.06. Social Cognition

**Support:** JST PRESTO JPMJPR1781
JSPS KAKENHI JP18H02544
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JSPS KAKENHI JP21H02593
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AMED JP21wm0525018

Naito Foundation
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**Title:** Conditional knockout of Shank3 by quantitative in vivo genome-editing in the ventral CA1 impairs social memory

**Authors: *M. CHUNG**[1,2], K. IMANAKA[1,2], Z. HUANG[1,2], A. WATARAI[1], M.-Y. WANG[1], K. TAO[1], H. EJIMA[3], T. AIDA[4], G. FENG[4,5], T. OKUYAMA[1,2];
[1]Inst. for Quantitative Biosci., Tokyo, Japan; [2]Grad. Sch. of Med., [3]Dept. of Materials Engin., The Univ. of Tokyo, Tokyo, Japan; [4]McGovern Inst. for Brain Res., MIT, Cambridge, MA; [5]Stanley Ctr. for Psychiatric Res., Broad Inst. of MIT and Harvard, Cambridge, MA

**Abstract:** Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition characterized by persistent deficits in social communication along with highly restricted, repetitive behaviors. One of the comorbidities frequently observed in Individuals with ASD is social memory impairment. A series of previous studies have shown that hippocampal ventral CA1 (vCA1) neurons and its microcircuits in the hippocampus are essential for social memory [1,2]. We recently reported that the neurophysiological representation of social memory in the vCA1 neurons is disrupted in ASD-associated SH3 And Multiple Ankyrin Repeat Domains 3 (*Shank3*) knockout mice [3]. However, it is still unclear whether the dysfunction of Shank3 in vCA1 causes the social memory impairment observed in ASD. In this study, we found that vCA1-specific *Shank3* conditional knockout (cKO) by the adeno-associated virus (AAV)- or specialized extracellular vesicle (EV)- mediated *in vivo* gene editing was sufficient to recapitulate the social memory impairment observed in individuals with ASD. Furthermore, the utilization of EV-mediated *Shank3*-cKO allowed for a quantitative examination of the role of *Shank3* in social memory. The results suggest that there is a certain threshold for the proportion of *Shank3*-cKO neurons required for social memory disruption. Our study provides insight into the population coding mechanism of social memory in vCA1, as well as the pathological mechanisms underlying social memory impairment in ASD. [1] Okuyama *et al.*, *Science* (2016); [2] Watarai *et al.*, *Curr Opin Neurobiol* (2021); [3] Tao *et al.*, *Mol Psychiatry* (2022)

**Disclosures:** **M. Chung:** None. **K. Imanaka:** None. **Z. Huang:** None. **A. Watarai:** None. **M. Wang:** None. **K. Tao:** None. **H. Ejima:** None. **T. Aida:** None. **G. Feng:** None. **T. Okuyama:** None.

**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR051.28/TT1

**Topic:** H.06. Social Cognition

**Support:** JSPS KAKENHI 22K06481
JSPS KAKENHI21H02593

**Title:** Non-linear encoding of social identity in mouse ventral hippocampus

**Authors: *K. TAO**, A. WATARAI, T. OKUYAMA;
Inst. for Quantitative Biosci., The Univ. of Tokyo, Bunkyo-City, Tokyo, Japan

**Abstract:** Social identity, characterized by the combination of multimodal information encompassing genetic, physical, and behavioral attributes, plays a crucial role in the recognition and interactions of individuals. In mice, neurons in the ventral hippocampus process a variety of behaviorally relevant information, store social memories of familiar individuals, and exhibit temporally organized activity patterns. However, the neural mechanisms by which these various social properties are integrated to represent social identity, particularly in terms of additive or interactive processes, remain unclear. In the present study, we implemented a social specification paradigm, facilitating interaction between the subject mouse and four familiarized conspecifics differentiated by strain and sex. By recording electrophysiological activity of ventral CA1 neurons using high-density 128-channel silicon probes while mice were performing the task, we revealed that a significant fraction of neurons exhibited non-linear responses to the presence of specific individuals. Through the analysis of neuronal population activities, we successfully decoded the strain, sex, and specific identity of the interacting conspecifics. These findings indicate that ventral hippocampal neurons encode multidimensional social information in an experience-dependent manner. Such encoding could substantially contribute to the organization of distinct dimensions within the hippocampal cognitive map.

**Disclosures:** **K. Tao:** None. **A. Watarai:** None. **T. Okuyama:** None.

**Poster**

**PSTR051. Circuits and Neural Mechanisms for Social Behavior**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

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**Topic:** H.06. Social Cognition

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The Naito Foundation
SECOM Science and Technology Foundation

**Title:** Ventromedial prefrontal neurons represent self-states shaped by vicarious fear

**Authors: *Z. HUANG**, M. CHUNG, K. TAO, A. WATARAI, M.-Y. WANG, H. ITO, T. OKUYAMA;
Univ. of Tokyo, Tokyo, Japan

**Abstract:** Perception of fear induced by others in danger elicits complex vicarious fear responses and behavioral outputs. In rodents, observing a conspecific receive aversive stimuli leads to escape and freezing behaviors. It remains unclear how these behavioral self-states in response to others in fear are neurophysiologically represented. In this study, we explored the function and neural representation of neurons in the ventromedial prefrontal cortex (vmPFC), an essential site for empathy, in an observational fear (OF) paradigm using male B6 mice (12-20 weeks old). To objectively classify the complex behaviors during OF, we employed DeepLabCut (DLC) with dimension reduction clustering using t-distributed stochastic neighbor embedding (t-SNE) and identified eight types of stereotypic behaviors. Optogenetic inhibition of the vmPFC specifically disrupted OF-induced escape behavior, but not freezing behavior. *In vivo* $Ca^{2+}$ imaging revealed that both stereotypic behaviors and freezing could be decoded from vmPFC neuronal activities. We identified two distinct neural subpopulations that are activated and suppressed when observing a demonstrator receiving foot shocks (i.e., other-shock). Neural activities of other-shock activated and suppressed neurons were negatively and positively correlated with self-freezing, respectively, revealing a mixed neural representation of other- and self-states in vmPFC neurons. By inhibiting the input from the anterior cingulate cortex (ACC) or basolateral amygdala (BLA) to the vmPFC during $Ca^{2+}$ imaging, we found that this mixed selectivity, or the representation of the self-state in the other-shock activated and suppressed neurons, required neural inputs from the ACC-vmPFC and BLA-vmPFC, respectively. Optogenetic inhibition of either the ACC-vmPFC or BLA-vmPFC resulted in the acceleration of escape behavior. Our study suggests that mixed population coding in vmPFC neurons represents self-states shaped by the other-state to elicit OF-induced escape behavior.

**Disclosures: Z. Huang:** None. **M. Chung:** None. **K. Tao:** None. **A. Watarai:** None. **M. Wang:** None. **H. Ito:** None. **T. Okuyama:** None.

**Poster**

**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR052.01/TT3

**Topic:** H.07. Long-Term Memory

**Support:** Irish Research Council 208243
Science Foundation Ireland 15/YI/3187
European Research Council 715968

**Title:** Adaptive expression of engrams by retroactive interference

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**Abstract:** Long-term memories are stored as stable configurations of neuronal ensembles, termed engrams. While investigation of engram cell properties and functionality in memory recall has been extensive, less is known about how engram cells are affected by forgetting. Here, we investigated a specific form of forgetting: retroactive interference. This occurs when new incoming information impairs the consolidation or retention of a recently encoded memory. By using activity-dependent cell labelling, we assessed the effect of retroactive interference on the formation, expression, and functionality of engram cells in the hippocampus dentate gyrus. We found that interference results in decreased engram cell reactivation during recall trials, and that optogenetic stimulation of the labelled engram cells is sufficient to induce memory retrieval following interference. Forgotten engrams may also be reinstated via the presentation of similar or related environmental information. Furthermore, we demonstrated that engram activity is necessary for interference to occur. Taken together, these findings indicate that forgetting modulates engram expression in a manner that is both reversible and updatable. Interference may constitute a form of adaptive forgetting, where in everyday life new perceptual and environmental inputs modulate the natural forgetting process.

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**Poster**

**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR052.02/TT4

**Topic:** H.07. Long-Term Memory

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**Title:** Immune activation state modulates the retrieval of infant engrams

**Authors: *S. D. POWER**[1,2,3], E. STEWART[2,3], L. G. ZIELKE[2,3,4], E. P. BYRNE[2], C. ORTEGA-DE SAN LUIS[2,3], L. LYNCH[2,5], T. J. RYAN[2,3,6,7];
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**Abstract:** Infantile amnesia, a pervasive form of memory loss in mammals, remains a complex and poorly understood phenomenon. The underlying biological conditions and effects on memory engrams are yet to be fully elucidated. We employed engram labeling technology and mouse models of infantile amnesia to investigate the neurobiology of this developmental memory loss. We discovered that male offspring in maternal immune activation models of autism spectrum disorder do not demonstrate infantile amnesia. Using optogenetic techniques, we successfully reactivated forgotten infantile memories by targeting engram cells in the dentate gyrus that were labeled during critical infant developmental experiences. Importantly, we demonstrate the reversible nature of infantile amnesia, by permanently reinstating lost memories through artificial manipulation of the memory engram. Lastly, we provide evidence that the effect of immune activation on infantile amnesia is mediated by the downstream effector cytokine IL-17a.

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**Poster**

**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR052.03/TT5

**Topic:** H.07. Long-Term Memory

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**Title:** Cold sensitive memory engrams control whole-body metabolism

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Melbourne, Australia; [5]Child & Brain Develop. Program, Canadian Inst. for Advanced Res. (CIFAR), Toronto, ON, Canada

**Abstract:** Environmental thermal challenges trigger the brain to coordinate both autonomic and behavioral responses in order to maintain optimal body temperature. It is unknown how temperature information is precisely stored in the brain, and how it is converted into a whole-body physiological response. Recent studies have shown that mental state can have an influence on bodily functions and that associative learning processes can modify peripheral immune and neuroendocrine responses. However, studies have yet to directly link a memory of a learned experience to immediate physiological changes in the body for host adaptability. We investigated whether memories can control whole-body metabolism by training mice to remember a thermal challenge. Animals were conditioned to associate a particular context with a specific temperature, by combining thermoregulatory pavlovian conditioning with engram labelling technology and optogenetic approaches. We found that if mice are returned to an environment where they previously experienced a cold-challenge, they increase their metabolic rates regardless of the actual environmental temperature. Moreover, mice develop a conditioned place aversion for the cold context, and avoid a cold environment if given the choice. Additionally, we show increased hypothalamic activity when animals are exposed to the cold, and that a specific network emerges between the hippocampus and the hypothalamus during the recall of a cold memory. Moreover, both natural retrieval and artificial reactivation of cold-sensitive memory engrams in the hippocampus mimic the physiological responses that are seen during a cold-challenge. Together, we demonstrate that retrieval of a cold memory causes whole-body autonomic and behavioral responses that enable animals to maintain thermal homeostasis.

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**Poster**

**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR052.04/TT6

**Topic:** H.07. Long-Term Memory

**Support:** RF1 NS121316
R01NS107370

**Title:** High Frequency Head Impact Eliminates Plasticity in the Memory Engram to cause Retrograde Amnesia

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**Abstract:** Frequent exposure to sub-concussive impacts is associated with memory impairments and increased risk of neurodegenerative disease, however, the mechanisms by which mild head impacts cause cognitive impairment, and whether lost cognitive functions can be regained, are not well understood. Here, we explore the neural mechanisms of retrograde contextual fear amnesia following high-frequency head impact (HFHI) in mice.
TRAP2/Ai32 transgenic mice express channelrhodopsin-2/EYFP fusion protein in c-Fos expressing neurons following novel memory exposure, allowing us to visualize the memory engram. While HFHI does not affect the size of the hippocampal memory engram, HFHI mice do have retrograde contextual fear amnesia. We found that dentate gyrus engram neurons in sham mice undergo synaptic plasticity when exposed to natural recall cues, including an increase in the AMPA:NMDA ratio, AMPA-weighted tau, and dendritic spine volume. This plasticity differentiates engram neurons from their surrounding non-engram counterparts. In contrast, HFHI engram neurons do not experience this plasticity, and have reduced engram reactivation and memory failure. To demonstrate that HFHI-induced contextual amnesia is caused by a failure of plasticity, we successfully used in vivo optogenetic stimulation to artificially activate the engram and drive memory recall in HFHI mice.
We determine that it is possible to reinstate a forgotten memory in the head impact brain and establish that chronic cognitive impairment after HFHI is a result of deficiencies in synaptic plasticity instead of a loss in neuronal infrastructure. Targeting synaptic plasticity may have therapeutic potential for treating memory impairments caused by repeated head impacts.

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**Poster**

**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

**Location:** WCC Halls A-C

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**Topic:** H.07. Long-Term Memory

**Support:** European Research Council 715968
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**Title:** Assessing the role of adhesion molecules for engram formation and memory function

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Melbourne, Melbourne, VIC, Australia; [6]Child & Brain Develop. Program, Canadian Inst. for Advanced Res. (CIFAR), Toronto, ON, Canada

**Abstract:** Learned information is translated into the brain as a subset of plastic changes that affect engram cells. The activation of engram cells is sufficient and necessary to recall a memory. It has been hypothesized that long-term information is stored through the specific connectivity patterns of engram cells across brain regions We investigated how the formation and function of engram cells is regulated by transsynaptic adhesion molecules. We focused on assessing the role of clustered protocadherins (cPcdhs), a superfamily of cell surface proteins that act as a barcode system for cell to cell recognition and synapse specification. Combining RNA detection tools and engram labelling technology we investigated how experiences are translated into cPcdh expression changes in the hippocampus. We further explored how manipulation of cPcdh expression influences behaviour and engram formation by combining engram labelling with loss of function mutant models. Altogether, our research supports that cPcdhs act as a molecular mechanism to determine memory formation and biology and influence engram function.

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**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

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**Topic:** H.07. Long-Term Memory

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AFOSR Grant
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**Title:** Overwriting an instinct: extinction and reinstatement of the innate threat response to visual looming stimuli

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**Abstract:** Behavioral neuroscience encompasses the study of both innate behaviors (instincts) and learned behaviors (memory). However, recent advances have challenged the notion of fixed

instincts, highlighting their potential for change through experience. This study investigated the plasticity of the innate defensive response to visual looming stimuli. We developed a visual looming paradigm where repeated exposure to visual looming stimuli resulted in a significant attenuation of defensive behavioral responses, akin to extinction learning. Interestingly, a single footshock was sufficient to reinstate these defensive responses. This behavioral paradigm allowed us to study what happens within the brain during "unlearning" of an innate behavior, and how a "relearned" behavior compares to an equivalent innate behavior. First, we examined the activity patterns of the superior colliculus (SC) and periaqueductal gray (PAG) by the expression of the immediate-early gene c-Fos. We found reduced c-Fos expression in the SC and PAG following extinction, and reduced correlation of c-Fos expression between these two regions. When behavioral responses were reinstated, there was recovery of c-Fos expression in the PAG, but the correlation in activity between SC and PAG was not recovered. To gain a deeper understanding of the neural dynamics, we performed in vivo calcium activity recordings in the SC and PAG using fiber photometric recordings of GCaMP fluorescence. Following extinction training, we observed a reduction in the response of the PAG to looming stimuli, while the SC response remained intact. This suggests that while threat detections in the SC persists across extinction, transmission of this information to the PAG is disrupted. Following reinstatement, the PAG remained unresponsive while the activity of the SC was suppressed during looming stimulus presentation. These findings suggest the existence of an alternative pathway beyond the canonical SC-PAG circuitry, mediating the reinstated behavioral response to visual looming stimuli. Overall, our study uncovers the experience-dependent plasticity of the innate looming response and provides insights into the underlying neural mechanisms. These findings have implications for understanding the interplay between instinctual and learned behaviors, paving the way for future investigations in adaptive behavior and memory processing.

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**Poster**

**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

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**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR052.07/TT9

**Topic:** H.07. Long-Term Memory

**Title:** A fear memory engram in the auditory cortex

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**Abstract:** Memory is supported by ensembles of neurons known as engram cells. These cells have been well characterized within the hippocampus and related brain regions, however little is known about the cellular properties of engram cells in sensory cortical areas. This study used

activity-dependant engram tagging technology, *in vivo* calcium imaging and patch clamp electrophysiology to characterize the somatic and dendritic properties of engram cells within the auditory cortex. Using tone fear conditioning in c-fos-tTA transgenic mice, we identify a population of layer 5 pyramidal neurons which are reactivated by natural tone memory recall. Moreover, optogenetically photoactivating these cortical engram cells induced freezing behaviour. *In vivo* calcium imaging revealed a decreased and synchronized pattern of evoked activity in the dendrites of engram cells during memory recall. *Ex vivo* patch-clamp recordings from cortical engram cells identified that Ih currents, key regulators of dendritic excitability, are increased in engram cells compared to non-engram cells. Taken together, these network and intrinsic properties combine to suggest that cortical engram cells may be critical to synchronize the evoked activity within the auditory cortex during memory recall.

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**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

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**Title:** Microglial Plasticity as a Modulator of Infantile Amnesia

**Authors: *E. STEWART**[1,2], L. G. ZIELKE[1,2], S. D. POWER[1,2,3], G. GUILLAUME-BOULAIRE[1,2,4], T. J. RYAN[1,2,5,6];
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**Abstract:** Infantile amnesia describes the inability to recall memories formed during a critical period of development in infancy and early childhood. The neurobiology of this highly conserved phenomenon remains poorly defined. Research in rodents has demonstrated that memories formed prior to the onset of infantile amnesia are not completely lost but rather maintained across the lifespan in a latent and inaccessible state. Furthermore, our previous work

has shown that immune challenge during pregnancy, maternal immune activation (MIA), prevents infantile amnesia in male offspring suggesting an important role of immune cells and signalling in the neurobiology of this phenomenon. Here, we characterised the mechanistic relationship between MIA, immune signalling, and infantile amnesia with a focus on microglial cells. Microglia, the resident immune cells of the brain, are known to play an important role in synaptic refinement during postnatal development and are also perturbed by MIA. We found that inhibition of microglial activity during a specific postnatal window prevents infantile amnesia for a contextual fear memory. We trained infant mice at postnatal day 17 on a contextual fear conditioning task and inhibited microglial activation using the tetracycline antibiotic minocycline. We then investigated the effect of microglial inhibition on recall of this fear memory 1 (pre-amnesia) and 8 (post-amnesia) days post-training. We found significantly elevated levels of freezing 8 days post-training in mice treated with minocycline compared to controls. Our results suggest that microglial activity during postnatal development may affect engram plasticity and memory accessibility. Using activity-dependent ensemble labelling, we have labelled infant memory engram cells and through histological analysis we have explored the characteristics and changes in these cells pre- and post-amnesia as well as characterising microglial structure across this critical postnatal window. To explore the overlap between MIA, microglia activity and infantile amnesia we are currently manipulating microglia in MIA offspring to elucidate the effect on memory, as well characterising microglial-engram interactions histologically and microglial gene expression both embryonically and postnatally following MIA. Our results suggest that microglia may play an important role in the neurobiology of infantile amnesia.

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**Poster**

**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

**Location:** WCC Halls A-C

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**Topic:** H.07. Long-Term Memory

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**Title:** Sleep replay improves performance of artificial neural networks when data are limited or unbalanced

**Authors: A. BAZHENOV**[1], P. DEWASURENDRA[1], *G. KRISHNAN[2], E. DELANOIS[2]; [1]Del Norte High Sch., San Diego, CA, CA; [2]Univ. of California San Diego, San Diego, CA

**Abstract:** The performance of artificial neural networks (ANNs) heavily relies on the availability of training data, which can be limited in certain domains. Additionally, training

datasets are often imbalanced, with some categories occurring more frequently than others, resulting in reduced accuracy of ANNs. In contrast, the human brain demonstrates the ability to learn quickly from just a few examples. It has been suggested that memory replay during biological sleep can strengthen memories learned during wakefulness. In this study, we investigated the role of sleep and its impact on improving the performance of ANNs trained with limited data. Initially, the ANN was trained on the MNIST dataset using backpropagation and subsequently mapped to a spiking neural network (SNN) with the same architecture, incorporating sleep. During the sleep phase, the SNN's activity was driven by randomly distributed Poisson spiking input, and synaptic weights were updated based on local Hebbian-type plasticity rules. After the sleep phase, the SNN was remapped back to the ANN, and its accuracy was evaluated again. When the ANN was trained with the full dataset, it achieved an accuracy of over 90%. However, when less than 10% of the data was used during training, accuracy significantly declined. We found that when only 2-10% of the data was used for ANN training, the sleep phase resulted in a substantial (20-30%) increase in accuracy. However, we also observed a slight (10-12%) decrease in performance when more than approximately 20% of the data was employed for ANN training. This decrease in performance could be mitigated by fine-tuning the ANN after sleep using the original (limited) training data. Thus, by incorporating both sleep and fine-tuning, we were able to maintain performance on models trained with the full dataset while still achieving performance gains on models trained with limited data. Next, we examined accuracy when a large class imbalance was introduced in the training set. Here, the sleep phase proved effective in increasing model accuracy on underrepresented classes while preserving accuracy on well-trained classes. Analysis of the confusion matrix revealed that networks trained with limited data can exhibit biases towards a few classes, whereas after sleep, they demonstrated a more balanced response. Overall, sleep increased the sparsity of responses by reducing synaptic weights. This study sheds light on a potential synaptic weight dynamics strategy employed by the brain during sleep to enhance memory performance when training data are limited or imbalanced.

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**Poster**

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**Title:** Understanding offline statistical learning: Consolidation of information in short waking rest periods after task

**Authors: *B. QUINTERO-MANES**[1], A. CHICA[2], E. CAMARA[3], R. DE DIEGO-BALAGUER[4];
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**Abstract:** Statistical learning (SL) involves extracting meaningful regularities by utilizing distributional information from the environment. While SL is typically studied in online tasks, there is evidence supporting the consolidation of learning and encoding during rest periods following tasks, even in short periods of waking rest (Wamsley, 2019 & 2022; Wamsley & Summer, 2020). Recent research suggests that short waking rest periods between tasks may aid in memory consolidation and learning decoding. This study aimed to explore the brain regions and networks associated with statistical learning and memory consolidation during short waking rest blocks following a statistical language learning task involving non-adjacent dependency rules. To achieve this, an fMRI experiment using an implicit measure of learning was conducted. The task involved detecting a target word within 3-word phrases, with language structures consisting of rule and no-rule patterns. Rule blocks followed an A-X-C structure, where "C" (the target word) was predicted by "A." No-rule blocks followed an X-X-C structure, with no predictor for "C." The experimental block was divided into three runs. In each run, two task conditions (Rule/NoRule) were presented, counterbalanced between participants, followed by two periods of walking rest (After Rule/After NoRule). Each task consisted of a 4 minutes block, followed by a 30 sec waking rest period. Each run was analyzed separately, considering different learning and waking rest stages. When comparing the waking rest periods following Rule and NoRule blocks in the first run, we observed higher activation in bilateral superior temporal lobe (STL), medial temporal lobe (MTL), and both hippocampi. In the second run, higher activations for the rest period following Rule were focused on the left MTL and right cerebellum. However, no significant differences were observed between Rule-waking rest and NoRule-waking rest in the last run. Comparing contrasts globally, both the rest periods following Rule and NoRule conditions showed higher activity in the first run compared to the second and third runs. This suggests a greater allocation of cognitive resource during the initial consolidation of rules during rest . Notably across all runs, the left MTL consistently showed activation. In conclusion, these preliminary results confirm that statistical learning and encoding continue after tasks, with brain activity during waking rest associated with learning and encoding (hippocampus, temporal lobe involved from early stages). The MTL seems to play a relevant role in consolidation during rest periods of statistical learning of non-adjacent dependencies.

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**Topic:** H.07. Long-Term Memory

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**Title:** Causal role of PFC-M1 coordination during long-term motor memory consolidation

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**Abstract:** Systems consolidation is a process by which new experiences are initially encoded in the hippocampus and subsequently transferred to the cortex, facilitating integration into long-term memory networks. Our recent study showed that the precise temporal dynamics of cross-area coupling between prefrontal cortex (PFC) and primary motor cortex (M1) can demarcate the transition to cortical stabilization and task performance, reducing involvement of the hippocampus. Here, we demonstrate the causal role of precise coupling in PFC-M1 sleep slow oscillation (SO) for motor memory stabilization. Using a skill learning task, we monitored cross-area coupling during NREM sleep and changes in reach-to-grasp motor task performance. Optogenetic interventions were applied to manipulate PFC-M1 SO coupling. Interestingly, disturbances in PFC activity during PFC-M1 coupled SO in sleep led to delayed increases in PFC-M1 coordination and slower stabilization of motor task performance - suggesting the causal impact of PFC-M1 coupling on evolving cortical representations during systems consolidation. Notably, the slower increases in PFC-M1 SO coupling were associated with disruptions and delayed enhancements of cross-area coupling during spindle trains, occurring in temporal clusters. Specifically, our results indicate that PFC SO could serve as predictors of the occurrence of M1 spindle trains. These results provide evidence for the causal role of PFC-M1 dialogue in memory representations during long-term motor learning and adaptation.

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**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

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**Title:** Environmental enrichment prevents the maintenance of LTP in the insular cortex

**Authors: *B. GUTIERREZ**, M. L. ESCOBAR RODRIGUEZ;
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**Abstract: Environmental enrichment prevents the maintenance of LTP in the insular cortex**
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It has been shown that exposure to an enriched environment (EE) can modulate the physiological impact of aversive stimuli in animals, promoting adaptive attitudes and the development of resilience to stressful situations. Likewise, it is known that EE can modulate synaptic plasticity, as is the case of long-term potentiation (LTP). Our previous studies have shown that prior training in conditioned taste aversion prevents the subsequent induction of LTP in the projection from the basolateral nucleus of the amygdala (Bla) to the insular cortex (IC) in vivo, as well as, that previous exposure to environmental enrichment is capable of reducing the strength of an aversive memory trace, restoring the brain-derived neurotrophic factor (BDNF) levels in a neocortical region of the adult brain. The aim of the present study was to analyze the effects of exposure to an enriched environment on the in vivo IC-LTP. To do so, adult rats were exposed to an EE before LTP induction in the Bla-IC pathway. Our results demonstrate that exposure to an EE allows induction but prevents maintenance of LTP in the insular cortex. These results provide evidence that exposure to an enriched environment promotes homeostatic regulation in a neocortical region of the adult brain.
Keywords: Environmental enrichment, Insular cortex, Amygdala, LTP, Homeostatic Plasticity.

**Disclosures: B. Gutierrez:** None. **M.L. Escobar Rodriguez:** None.

**Poster**

**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR052.13/TT14

**Topic:** H.07. Long-Term Memory

**Support:** NIH R56 Grant MH104589
NIH R21 Grant MH128802

**Title:** Fear extinction alters brain-wide cell activation following contextual fear conditioning

**Authors: *F. ZAMUDIO**, P. SCHAMBER, L. G. REIJMERS;
Neurosci., Tufts Univ., Boston, MA

**Abstract:** Memories are thought to be stored in the brain in engrams, that is, neurons active during initial memory acquisition that are then re-activated during the memory retrieval process.

Fear memory engrams, in particular, have been found to be present throughout the whole brain in mice, indicative of a fear memory circuit responsible for the storage and retrieval of that memory. However, the brain region connectivity between fear engram containing regions has not been completely elucidated. Additionally, there is no brain-wide dataset targeted towards research of brain regions involved in suppression of fear memories through exposure therapy. In order to advance research in the field, we labeled engrams in TetTag mice during contextual fear conditioning and divided them into two groups, one which received a single contextual retrieval trial and one which underwent extinction training through repeated contextual exposure followed by a final contextual retrieval trial. Ninety minutes after the last contextual retrieval in both groups, mice were sacrificed, and their brains collected for brain-wide engram reactivation analyses and cell activation using the immediate-early gene zif-268. As expected, our results confirm that fear engram reactivation within the basal amygdala is reduced following fear extinction in mice. Further, most importantly, our data reveals altered brain region activation following fear extinction training, as well as shows putative brain region connectivity during fear retrieval as well as fear extinction memory retrieval through network analyses.

**Disclosures: F. Zamudio:** None. **P. Schamber:** None. **L.G. Reijmers:** None.

**Poster**

**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR052.14/TT16

**Topic:** H.07. Long-Term Memory

**Support:** KL2 TR001862
K01 AA027832

**Title:** Dynamic brain mechanisms supporting salient memories under cortisol

**Authors: *Y. HUANG**, D. O'CONNOR, B. HARRIS, R. SINHA, R. T. CONSTABLE, E. V. GOLDFARB;
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**Abstract:** Stress-induced increases in cortisol can enhance encoding for individual emotionally salient experiences. Yet most work examining cortisol's effect on memory has focused on negative effects and pre-defined brain regions. Here we aimed to define whole-brain mechanisms by which cortisol enhances memories for individual experiences. We developed a novel analytic approach by combining dynamic metrics of whole-brain connectivity with connectome-based predictive modeling (CPM). This approach enabled us to capture neural mechanisms supporting memory and arousal states that fluctuate on a trial-by-trial basis.
Data was collected using a double-blind, placebo-controlled, within-subjects design. Participants (N = 26) encoded associations between photographs of objects and scenes during 2 fMRI runs (N = 40 trials/run; 1 run = emotional, 1 run = neutral). Memory was assessed 24hr later. Participants

completed this twice, once receiving 20 mg hydrocortisone prior to encoding and once receiving a placebo, resulting in a 2x2 design combining emotionality (neutral vs emotional) and pharmacology (cortisol vs placebo). Subjective arousal during encoding and memory success were recorded per trial.
Consistent with our hypothesis, cortisol enhanced memory for emotionally salient objects ($p=.01$). To understand trial-level neural mechanisms underlying this benefit, we divided the brain into nodes (Goldfarb et al., 2022) and applied Hilbert transformation to derive whole-brain phase synchrony between all node pairs per trial. Using CPM, we predicted trial-level memory and arousal with phase synchrony and successfully derived predictive networks under each emotional and pharmacological condition (all $ps < .001$). We then examined the function and architecture of these memory-predictive and arousal-predictive networks. Generally, arousal networks had stronger engagement and more overlaps under cortisol while memory networks were stronger and overlapped more under placebo. Critically, we found that shared neural resources promote both arousal and memory under cortisol but not placebo. First, there was more overlap between memory and arousal network edges under cortisol than placebo. Second, the memory-predictive network could generalize to track trial-level arousal under cortisol, but not placebo. Finally, we observed greater coherence between memory-predictive and arousal-predictive networks throughout runs encoded under cortisol than placebo.
Together, the above results indicate that cortisol promotes integration of widespread neural networks supporting memory and arousal, thus potentiating the formation of emotionally salient memories.

**Disclosures:** **Y. Huang:** None. **D. O'Connor:** None. **B. Harris:** None. **R. Sinha:** None. **R.T. Constable:** None. **E.V. Goldfarb:** None.

**Poster**

**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR052.15/TT17

**Topic:** H.07. Long-Term Memory

**Support:** NIH Grant MH104384

**Title:** Posttraining optogenetic inhibition of basolateral amygdala projections to the nucleus accumbens shell impairs inhibitory avoidance and cued-response retention in rats

**Authors: *B. GLICKMAN**[1], K. L. WAHLSTROM[2], R. T. LALUMIERE[1,2,3];
[1]Interdisciplinary Grad. Program in Neurosci., [2]Dept. of Psychological and Brain Sci., [3]Iowa Neurosci. Inst., Univ. of Iowa, Iowa City, IA

**Abstract:** The basolateral amygdala (BLA) and nucleus accumbens (NA) play critical roles in modulating the consolidation of inhibitory avoidance (IA) and cued-response learning. Prior research suggests that bilaterally disconnecting the BLA and NA blocks the memory-enhancing

effects of posttraining synthetic glucocorticoids on IA retention. Furthermore, concurrent dopamine release in the BLA and NA shell after training is required to modulate IA retention. Regarding cued-response learning, stimulating the BLA-medial entorhinal cortex pathway after training impairs cued-response retention, though the pathway that positively modulates this learning is unknown. However, previous research indicates that the BLA and NA are involved in other types of cued learning such as cued sucrose and cued alcohol seeking. Together, this points to the idea that these structures likely interact to modulate both IA and cued-response memory consolidation, yet it is unknown whether the BLA-NA shell pathway is the mechanism by which this modulation occurs. To address this question, male and female Sprague-Dawley rats were given intra-BLA AAV injections containing the inhibitory opsin eNpHR3.0 under the control of the CaMKIIα promoter and then optical fiber implants were aimed at the NA shell. For IA experiments, rats underwent a 2-min pre-exposure trial where they freely explored the IA apparatus and, 24 h later, were trained on a single-trial step-through IA task. For cued-response experiments, rats underwent four consecutive training trials on a Barnes maze in which a single intra-maze cue indicated the correct escape port. Immediately after training on either task, rats received 15 minutes of optical inhibition of the BLA-NA shell pathway. Retention testing occurred 48 h after training, and latency to enter the shock compartment (IA) or latency to find the escape port and duration spent in the target quadrant of the maze (cued Barnes maze) were measured. Results revealed that rats that received inhibition of the BLA-NA shell pathway immediately after training had decreased latencies to cross into the shock compartment at the IA retention test. Similarly, at the cued Barnes maze retention test, animals that received inhibition had increased latencies to find the escape port and decreased time spent in the target quadrant of the maze. Together, these findings indicate that inhibiting this pathway after training impaired consolidation for both types of learning. Ongoing experiments are examining whether stimulating this pathway immediately after training modulates retention.

**Disclosures:** **B. Glickman:** None. **K.L. Wahlstrom:** None. **R.T. LaLumiere:** None.

**Poster**

**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR052.16/TT18

**Topic:** H.07. Long-Term Memory

**Support:** NSERC
CIHR
FRQS

**Title:** The nucleus reuniens mediates memory generalization during hippocampo-cortical coupling in sleep

**Authors: *D. BASHA**, I. TIMOFEEV;
Faculté de médecine, Univ. Laval, Quebec, QC, Canada

**Abstract:** Consolidated memories are characterized by a degree of generalization and abstraction of prior experience. The nucleus reuniens of the thalamus plays a key role in controlling memory generalization, thanks to its bidirectional connections with the hippocampus and the medial prefrontal cortex (mPFC). The synchronization of hippocampal sharp wave ripples (SWRs) and mPFC slow oscillations during sleep is essential for hippocampo-cortical communication and is thought to be the central mechanism by which specific recent experiences are integrated into existing neocortical networks. Here, we test the hypothesis that the generalization of memory is regulated by the reuniens during the coupling of hippocampal SWRs and mPFC slow waves in sleep. Combining fear conditioning, closed-loop optogenetic manipulations, spike/local field potential recordings and in vivo intracellular recordings in mice, we show that the generalization of contextual fear memory depends on the activity of the reuniens during sleep. Transient optogenetic silencing of the reuniens during SWRs enhanced the specificity of contextual fear memory but did not affect cued fear memory. Reuniens firing was significantly increased when hippocampal SWRs were followed by prefrontal slow waves in comparison to weakly-coupled SWR-slow waves. In vivo intracellular recordings of the mPFC and the thalamus showed that hippocampal SWRs drive synaptic activity within a subset of cells in the nucleus reuniens and in mPFC neurons. SWRs were associated with the emergence of local active states in the mPFC that preceded thalamic inhibition in the mediodorsal, ventromedial, ventrolateral and centromedian nuclei. We conclude that, by mediating the communication of hippocampal SWRs to the mPFC, the reuniens controls the progressive integration of specific experiences replayed during SWRs into generalized schemas represented in the prefrontal network.

**Disclosures:** **D. Basha:** None. **I. Timofeev:** None.

**Poster**

**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR052.17/TT19

**Topic:** H.07. Long-Term Memory

**Support:** JST ERATO JPMJER1801
Institute for AI and Beyond of the University of Tokyo
JSPS Grants-in-Aid for Scientific Research 18H05525

**Title:** Membrane potentials of retrosplenial late-spiking neurons are not locked with neocortical slow oscillations

**Authors: *H. MIZUNO**[1], Y. IKEGAYA[1,2];
[1]Grad. Sch. of Pharmaceut. Sci., [2]Inst. for AI and Beyond, The Univ. of Tokyo, Tokyo, Japan

**Abstract:** Memories acquired during wakefulness are consolidated during slow-wave sleep. This process involves the interplay between the hippocampus and the neocortex. Specifically, the

coupling of hippocampal ripples (100-250 Hz) and neocortical slow waves (-1 Hz) is crucial for memory consolidation, but the specific region that mediates this interaction has not yet been disclosed. One candidate is the retrosplenial cortex (RSC), which is connected to both the hippocampus (or subiculum) and the neocortex. Indeed, hippocampal ripples are transmitted to the RSC; however, the characterization of slow wave activity in the RSC remains to be elucidated. The RSC contains two distinct populations of excitatory neurons with different intrinsic membrane properties: i) regular-spiking neurons, which are prevalent in the other neocortical regions, and ii) late-spiking neurons, which are found only in some regions such as the RSC. To describe the activity of each cell type during slow waves, we used in vivo whole-cell patch-clamp recordings to monitor the membrane potentials of RSC neurons in urethane-anesthetized mice, together with local field potential recordings of slow waves. We determined the cell type by measuring the intrinsic membrane properties of individual cells. Out of a total of 40 neurons recorded, 21 neurons exhibited UP/DOWN membrane potential dynamics that were synchronized with slow waves, while 19 neurons displayed brief and frequent depolarizations that were not phase-locked to neocortical slow waves. Analysis of the intrinsic membrane properties revealed that the non-synchronized neurons were late-spiking neurons, whereas typical UP/DOWN cells were regular-spiking neurons. These data suggest that late-spiking neurons receive inputs from areas outside the neocortex, most probably hippocampus-relevant regions, while regular-spiking neurons receive inputs from the neocortex. This finding implies parallel processing of these two inputs in the RSC.

**Disclosures: H. Mizuno:** None. **Y. Ikegaya:** None.

**Poster**

**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR052.18/TT20

**Topic:** H.07. Long-Term Memory

**Title:** Desipramine reverses remote memory deficits by activating calmodulin-CaMKII pathway in a Utx knockout mouse model of Kabuki syndrome

**Authors: *Y. LI**;
Shanghai Jiao Tong Univ., shanghai, China

**Abstract:** Authors: Yuting Li, Xu Zhang, Lei Chen, Zhaohui Lan, Weidong Li*Kabuki syndrome is a rare developmental disorder characterized by multiple congenital anomalies and intellectual disability. UTX, which encodes a histone demethylase, is one of the two major pathogenic risk genes for Kabuki syndrome. To investigate how UTX regulates cognition, we generated Utx conditional knockout mice and found that Utx deletion downregulated calmodulin transcription by disrupting H3K27me3 demethylation. Importantly, Utx knockout mice showed decreased phosphorylation of CaMKII, impaired LTP and deficit in remote contextual fear memory, all of which could be rescued by an FDA-approved drug desipramine. We use the cFos-

ERT2CreERT2 x UTX-flox mice to investigate the mechanism of UTX during different periods of long-term memory. We also performed whole-brain engram network tracing for different stages of long-term memory.

**Disclosures: Y. li:** None.

**Poster**

**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR052.19/TT21

**Topic:** H.07. Long-Term Memory

**Support:** (NSERC) Discovery grant 2016-06576
(NSERC) Discovery grant 2021-02926

**Title:** Inhibition of protein synthesis with the amnestic agent emetine causes robust neural suppression

**Authors: *S. Z. AL-SMADI**[1], A. PADROS[2], G. G. GOSS[3], C. T. DICKSON[1,4,2,5]; [2]Neurosci., [3]Biosci., [4]Psychology, [5]Anesthesiol. and Pain Med., [1]Univ. of Alberta, Edmonton, AB, Canada

**Abstract: Inhibition of protein synthesis with the amnestic agent emetine causes robust neural suppression** Memory consolidation has been studied for over one hundred years, yet the biological mechanisms remain enigmatic. A nearly axiomatic idea in the field of neuroscience is that, ultimately, the fixation of the synaptic changes thought to represent learning processes in the brain is completely dependent on the production of new proteins. This conjecture relies mainly upon behavioural studies of memory function using inhibitors of protein synthesis. However, growing evidence has shown that there are serious confounding influences of these types of drugs that might, in and of themselves, cause memory loss. Such effects include severe impairment of neurobiological function, including induction of apoptosis, disruption of synaptic release, and the inactivation of neural activity. Our lab has previously provided clarifying evidence on the inactivating effects related to the use of translational inhibitors. Intrahippocampal infusions of either anisomycin or cycloheximide at concentrations previously shown to induce amnesia were shown to produce profound and long-lasting silencing of synaptic and post-synaptic activity that was correlated with the extent of protein synthesis inhibition. In this study, we evaluated the impact of intrahippocampal administration of another translation inhibitor, emetine, on neural activity. Results indicated a marked reduction in hippocampal neural activity following a modest inhibition of protein synthesis, as measured by autoradiographic techniques. A correlation was observed between the extent of inhibition of protein synthesis and the magnitude of disruption in neural activity.

**Disclosures: S.Z. Al-Smadi:** None. **A. Padros:** None. **G.G. Goss:** None. **C.T. Dickson:** None.

**Poster**

**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR052.20/TT22

**Topic:** H.07. Long-Term Memory

**Support:** NIH Grant NS132230
AHA Award Number: 1019413

**Title:** Astrocyte calcium tunes the strength of a fear memory

**Authors: *M. R. WILLIAMSON**, U. KWON, J. WOO, B. DENEEN;
Baylor Col. of Med., Houston, TX

**Abstract:** Astrocytes have a variety of functions that are critical for proper brain function. There is increasing evidence for roles of astrocytes in regulating circuit function. Many functions of astrocytes are mediated at least in part through their dynamic calcium activity. We investigated the effects of manipulating hippocampal astrocyte calcium during contextual fear conditioning on subsequent memory recall. We used viral tools in adult mice of both sexes to enhance or abolish calcium activity during learning (sample sizes at least six per group). Increasing astrocyte calcium enhanced recall of the contextual fear memory (measured by freezing behavior), whereas abolishing astrocyte calcium worsened recall. These behavioral effects were accompanied by corresponding increases or decreases in reactivation of the neuronal ensembles that were active during learning. Ongoing experiments are examining transcriptional dependencies of this function of hippocampal astrocytes. These results add to our understanding of the ways in which astrocytes regulate circuit function.

**Disclosures: M.R. Williamson:** None. **U. Kwon:** None. **J. Woo:** None. **B. Deneen:** None.

**Poster**

**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR052.21/TT23

**Topic:** H.07. Long-Term Memory

**Support:** NSF 2209874
NSF 2223839
NIH 1R01MH125557

**Title:** Hippocampal indexing during sleep prevents catastrophic forgetting by constraining the network to evolve along memory manifolds

**Authors: *E. DELANOIS**[1], O. C. GONZALEZ[2], R. GOLDEN[3], M. BAZHENOV[3];
[1]UCSD, San DiegoSan Diego, CA; [2]Dept. of Psychiatry and Behavioral Sci., Stanford Univ., Stanford, CA; [3]Univ. of California San Diego, La Jolla, CA

**Abstract:** Continual learning is foundational to human intelligence. Not only do we learn with minimal forgetting, but we learn better when new information is related to past knowledge to improve upon the representations of both. Sleep has been shown to play a critical role in memory consolidation in biological systems, and it is thought that interactions between the cortex and hippocampus provide a substrate for these processes. Using biophysical models of the cortex, we previously demonstrated periods of sleep can recover performance on memories following retroactive interference induced by sequential training of competing tasks. Here we expand on this by developing the idea of "memory manifolds" which describe various synaptic weight states which robustly represent specific memories to show how sleep evolves the network through this landscape. This framework revealed that sleep applied after sequential tasks training evolves the network towards one of multiple attractors on the memory manifold (i.e. representing each task independently, and representing a joint-task state), which are stable under sleep dynamics. While, in principle, capable of reaching a state supporting both memories, this continual learning strategy requires fine-tuning the training durations, and evolving the network through "off-manifold" regions of synaptic weight space (i.e. regions where the network could not perform well on either task). To mitigate these issues, we took inspiration from Systems Consolidation Theory, and implemented a model of hippocampal indexing by providing input, encoding the new memory, to the cortex near the Down-to-Up state transition of each slow wave. This forced the cortex to replay the new memory at the beginning of each Up state during sleep, while the old memory was still replayed during later phase of Up state. Under this protocol, the network was able to reliably encode the new memory while the initial memory was being further consolidated simultaneously. In other words, including hippocampal indexing changed the evolution of the network under sleep dynamics to ensure that it always remained "on-manifold". These results emphasize the importance of balancing old and new memory replays to ensure that the new memory is embedded into the cortical network structure without erasing the old ones. Hippocampal indexing changes how the network encodes the new memory, restricting the network to trajectories which stay "on-manifold", and converging on significantly sparser solutions (i.e. synaptic weight matrices) than can be attained through sequential training and sleep protocols.

**Disclosures: E. Delanois:** None. **O.C. Gonzalez:** None. **R. Golden:** None. **M. Bazhenov:** None.

**Poster**

**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR052.22/TT24

**Topic:** H.07. Long-Term Memory

**Support:** NIH 1R01NS109553
NIH 1R01MH117155

**Title:** Effect of long-range synaptic connectivity on sleep slow waves in a thalamocortical network model of the human brain

**Authors: *G. NAVAS**[1,2], B. M. MARSH[3,2], B. Q. ROSEN[3], Y. SOKOLOV[2], J. DELANOIS[4,2], O. C. GONZÁLEZ[2], G. P. KRISHNAN[2], E. HALGREN[5,3], M. BAZHENOV[2,3];
[2]Dept. of Med., [3]Neurosci. Grad. Program, [4]Dept. of Computer Sci. and Engin., [5]Departments of Radiology and Neurosci., [1]UCSD, La Jolla, CA

**Abstract:** Cortical slow (< 1Hz) oscillation (SO) dominates stage 3 of non-rapid-eye-movement (NREM) sleep. It consists of alternating Up and Down states and is believed to play a critical role in memory consolidation. While the properties of large-scale brain activity during SO have been described through magneto-/electro-encephalography (M/EEG) and local-field-potential (LFP) recordings, how macro-scale SO emerges from the interaction between micro-scale neuronal dynamics and cortical network connectivity is still poorly understood.
To bridge this gap, we developed a multi-scale, "whole-brain", computationally efficient thalamocortical network model that exhibits the essential activity states of NREM sleep. The model has ~10,200 cortical columns equally positioned across the surface of one hemisphere. Each column has pyramidal and inhibitory neurons arrayed in 6 layers. Intra-columnar connections follow the canonical cortical circuit. The modeled thalamus has ~640 columns, each with a matrix and core element comprised of thalamo-cortical and reticular neurons. Long-range cortical connectivity is based on DTI tractography between parcels determined by the Human Connectome Project, originating and terminating in layers according to the parcel's relative hierarchical positions. To investigate the role of connectivity in emerging SO, we modified the range and density of cortical connections, as well as synaptic weights and distance-dependent synaptic delays, and quantified their effect on the resulting large-scale slow-wave dynamics.
We found that sparser networks have reduced overall activity and generate waves with lower frequency and amplitude. A similar outcome is observed when weakening synaptic weights, but with a stronger effect on frequency than amplitude. In both cases, synchronized Up and Down states are maintained across the cortex. In contrast, as connection range is reduced, specific regions exhibit local SO that fail to spread through the cortex. This results in reduced global SO amplitude, although frequency stays relatively unchanged. Increasing synaptic delays also leads to oscillations with lower amplitude and less synchronized onsets and offsets.
Our results highlight the role of connection density and strength in maintaining and timing cortical activity during SO. We found that local connections can generate local slow waves, while long-range connectivity plays a critical role in generating global SO dynamics. Our innovative multi-scale model of the entire brain elucidates how the global structure of intracortical connections gives rise to the spatio-temporal properties of sleep SO.

**Disclosures: G. Navas:** None. **B.M. Marsh:** None. **B.Q. Rosen:** None. **Y. Sokolov:** None. **J. Delanois:** None. **O.C. González:** None. **G.P. Krishnan:** None. **E. Halgren:** None. **M. Bazhenov:** None.

**Poster**

**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR052.23/TT25

**Topic:** H.07. Long-Term Memory

**Support:** NSF Grant 2209874
NSF Grant 2223839
NIH Grant 1R01MH125557

**Title:** The phase of the cortical slow oscillation determines whether hippocampal sharp-wave ripples can bias cortical consolidation

**Authors: *R. GOLDEN**[1], O. C. GONZALEZ[2], M. TATSUNO[3], B. MCNAUGHTON[4], M. BAZHENOV[5];
[1]Univ. of California San Diego, La Jolla, CA; [2]Dept. of Psychiatry and Behavioral Sci., Stanford Univ., Stanford, CA; [3]Dept. of Neurosci., Univ. of Lethbridge, Lethbridge, AB, Canada; [4]Univ. of California, Irvine, Irvine, CA; [5]UCSD, La Jolla, CA

**Abstract:** Systems Consolidation Theory posits that the hippocampus encodes new information for cortical consolidation during non-REM sleep. Specifically, phase locking of cortical slow oscillations (SOs) and hippocampal sharp-wave/ripples (SWRs) is thought to allow for hippocampal replay of recent memories which index corresponding cortical traces to be replayed for long-term storage. Despite the success of Systems Consolidation Theory in explaining many experimental findings regarding how consolidation is coordinated, many of its central predictions remain untested. To understand the details of this coordination, we analyzed single-unit activity from the medial prefrontal cortex (mPFC) and CA1 of the hippocampus from rats trained to run a spatial sequence memory task. First, we analyzed the distribution of SWR times and found they tend to occur immediately after the down-to-up transition of SOs. To investigate how this phase preference affects the efficacy of hippocampal indexing, we developed a biophysically-realistic thalamocortical network model capable of transitioning between awake and sleep states, and equipped with spike-timing-dependent plasticity between pyramidal cells. Using this model, we systematically applied artificial indexing cues at various phases of the SO to assess the relationship between the phase of the SO when indexing occurs and the extent of synaptic consolidation. We found that the phase interval which facilitated robust synaptic consolidation was contained within the preferred phase for SWR arrival times, i.e., immediately after the down-to-up transition of SOs. Next, we focused on characterizing this preferred phase. We found that the von Neumann entropy of the cortical activity is a suitable proxy to measure transient sensitivity to external perturbations, while the PC dimension can capture persisting effects of the perturbation throughout a SO. Using these measures, we found evidence that SWRs can transiently bias cortical activity during any phase of the cortical SO, but there is an optimal phase just after the down-to-up transition during which SWRs can maximally bias persistent activity and drive robust consolidation. Importantly, our results indicate that von Neumann entropy may be employed to distinguish experimentally-relevant SWRs (i.e. SWRs that affect the activity of the particular cortical region being recorded) from experimentally-irrelevant ones. Thus, our

findings provide a functional and computational account for SO-SWR phase-locking - maximizing consolidation by ensuring SWRs arrive during a phase of SO in which the cortex is most responsive to incoming signals.

**Disclosures: R. Golden:** None. **O.C. Gonzalez:** None. **M. Tatsuno:** None. **B. McNaughton:** None. **M. Bazhenov:** None.

**Poster**

**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR052.24/TT26

**Topic:** H.07. Long-Term Memory

**Support:** NIH T32MH019524
NIH NS034007
NIH NS122316

**Title:** Astrocytes secrete factors that upregulate neuronal protein synthesis

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

**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 by spiking into the medium puromycin, an aminonucleoside that enters the ribosomal A site to transfer to a growing peptide, leading to premature chain termination and release. Neurons treated with ACM displayed increased puromycin signal, suggesting that astrocytes release factors that increase neuronal protein synthesis. In addition, the upregulation in *de novo* protein synthesis was further increased by treating the astrocytes with brain-derived neurotophic factor (BDNF) prior to ACM collection. BDNF-treated astrocytes did not display increased puromycin signal, suggesting that the increased neuronal protein synthesis is dependent on the upregulation of specific astrocyte-secreted factors, rather than an increase in overall astrocyte protein synthesis. Taken together, these findings suggest that astrocytes can regulate neuronal protein synthesis in a physiological, non-cell autonomous manner that may be important for long-lasting synaptic plasticity and memory. Moreover, disruption of this astrocyte-neuron communcation might underlie impaired protein synthesis observed in neurodegenerative diseases such as Alzheimer's disease. This work was supported by NIH grants T32MH019524 (W.J.L), NS034007 and NS122316 (E.K.).

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

**Poster**

**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR052.25/TT27

**Topic:** G.01. Fear and Aversive Learning and Memory

**Support:** Columbia University RISE Award

**Title:** Investigating the Epigenetic Mechanisms underlying Memory Consolidation during Sleep

**Authors:** ***X. CHEN**[1], J. HWANG[2], B. A. UCEDA-ALVAREZ[3], L. YAO[6], A. N. M. RODRIGUEZ[3], S. LIU[4], Y. PENG[5];
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**Abstract:** Sleep after learning something ("post-learning sleep") actively consolidates what was learned. Yet, the underlying cellular and molecular mechanisms remain elusive. In this study, we combine *in vivo* calcium imaging, optogenetic manipulation, sleep recording, DNA sequencing technologies, and mice behavior assays to examine how epigenetic mechanisms such as DNA methylation contributes to the memory consolidation process during sleep. We focus on the basolateral amygdala (BLA) complex, an important memory storage site (i.e. memory engram) but a poorly studied brain region for its neuronal activity during sleep and its memory-related epigenetic changes. Here, we present our preliminary data showing that: (1) BLA neurons show increased activity during REM sleep, compared to that in non-REM (NREM) sleep; (2) a sub-group of BLA neurons are active at the time of receiving foot shock in the fear conditioning memory paradigm; (3) BLA neurons have more synchronized activity during post-fear conditioning learning sleep; (4) inhibiting BLA during post-fear conditioning learning rapid eye movement (REM) sleep might impair memory performance; (5) a DNA methyltransferase, DNMT3A, in the memory engram cells is necessary for proper memory recall function. In conclusion, our data suggest that epigenetic changes and BLA activity during post-learning REM sleep are important for fear memory consolidation.

**Disclosures:** **X. Chen:** None. **J. Hwang:** None. **B.A. Uceda-Alvarez:** None. **L. Yao:** None. **A.N.M. Rodriguez:** None. **S. Liu:** None. **Y. Peng:** None.

**Poster**

**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR052.26/TT28

**Topic:** H.07. Long-Term Memory

**Support:** CIHR FDN- 148423

**Title:** Activating transcription factor 4 (ATF4) controls memory consolidation in a cell-type specific manner

**Authors:** ***N. MAHMOOD**, J.-H. CHOI, Z. HUANG, V. SHARMA, N. SONENBERG;
McGill Univ., MONTRÉAL, QC, Canada

**Abstract:** Regulation of proteostasis is a crucial rate-limiting step during memory consolidation. The evolutionarily conserved integrated stress response (ISR) pathway regulates proteostasis by tuning protein synthesis in response to intracellular stress and thereby functions as a central molecular switch promoting the formation of long-term memories. Previous studies have shown that inhibiting the phosphorylation of the α-subunit of eIF2 (p-eIF2α), the main component of the ISR, by genetic and pharmacologic manipulations improves memory formation. However, the role of activating transcription factor 4 (ATF4), the major downstream effector of ISR that is translationally upregulated upon stress-induced phosphorylation of eIF2α due to the presence of upstream open reading frame, in memory consolidation is not precisely known. To this end, we used molecular genetics to knockout *Atf4* in excitatory and inhibitory neurons and confirmed its cell-type-specific depletion by dual RNA in situ Hybridization (ISH) and Immunohistochemistry (IHC). We found that *Atf4* depletion in the excitatory neurons, which comprises the largest percentage of the neuronal cells in the neocortex, enhanced contextual fear memory in mice. Biochemical analyses of the synaptic proteins extracted from the excitatory neuron specific *Atf4* knockout mice showed enrichment of several postsynaptic density proteins compared to the controls. Taken together, our study demonstrates that the inhibition of the ISR effector, ATF4, in excitatory neurons promotes long-term memory formation.

**Disclosures:** **N. Mahmood:** None. **J. Choi:** None. **Z. Huang:** None. **V. Sharma:** None. **N. Sonenberg:** None.

**Poster**

**PSTR052. Consolidation and Reconsolidation: Molecular and Circuit Mechanisms**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR052.27/UU1

**Topic:** H.07. Long-Term Memory

**Support:** NIH Grant P20GM103423

**Title:** Tet enzyme degrader bobcat339 enhances spatial memory in mice

**Authors:** E. BARNES, A. REARDON, ***A. J. KENNEDY**;
Neurosci., Bates Col., Lewiston, ME

**Abstract:** Active DNA methylation in neurons following learning is necessary for long-term memory formation. Therefore, DNA de-methylation through TET mediated enzyme activity is associated with enhancements in memory fidelity. Here, we show that reducing TET enzyme activity in memory circuits and engrams enhances spatial and social memory. Using a conditional Tet2 KO allele and activity-dependent Cre drivers, Tet2 knockout in engram cells was found to enhance the lifetime of memory in mice, using long-term object location memory and social memory tasks. Additionally, the single dose of Bobcat339, a small molecule Tet enzyme degrader, was sufficient to enhance spatial memory in mice, suggesting therapies that target the Tet enzymes might be used to enhance memory function.

**Disclosures: E. Barnes:** None. **A. Reardon:** None. **A.J. Kennedy:** None.

**Poster**

**PSTR053. Learning and Memory: Hippocampal Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR053.01/UU2

**Topic:** H.08. Learning and Memory

**Support:** NINDS/NIH T32 NS-45540

**Title:** Hippocampal sharp wave ripple dynamics in a reward devaluation task

**Authors: *B. L. BOUBLIL**[1], G. TARCSAY[1], G. IRIZARRY-MARTINEZ[2,3], N. MASALA[1], C. B. DANG[1], L. A. EWELL[1,3], M. SABARIEGO[4];
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**Abstract: Hippocampal sharp wave ripple dynamics in a reward devaluation task**

Brittney L. Boublil[1*], Gergely Tarcsay[1], Gimarie Irizarry-Martinez[2,3], Nicola Masala[1], Cathy B. Dang[1], Laura A. Ewell[1,2], and Marta Sabariego[4]
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**Abstract:**
In the wild, locating and remembering the location of a food source is critical for survival, as well as the ability to adapt when the availability of that food source changes. The hippocampus exhibits reward-related firing at reward locations. However, the neural mechanisms underlying how the hippocampus might represent changes in other aspects related to a reward, such as value (i.e., quantity and quality), remains unclear. In our study, mice (N = 13; 9 females, 4 males) learn there is a large reward (30 uL sucrose) on one side of a figure-8 maze and a small reward (5 uL

sucrose) on the other (large reward preference: 84.23% +/- 1.58). After showing a preference (3-4 days), the large reward is devalued to 5 uL (i.e., both reward sides are equal) while the small reward is maintained stable for the duration of the experiment (preference for devalued side: 68.21% +/- 3.87). Mice that did not demonstrate significant adaptation to the reward downshift went through an additional extinction phase (preference for extinguished side: 42.5% +/- 5.95). To assess neural mechanisms of adjustment to reward devaluation, we performed high-density, single-unit recordings in hippocampal CA1 in mice (N = 4; 2 females, 2 males). Our data point towards a two-fold increase in sharp wave ripple (SWR) rate during post-behavior sleep sessions following the devaluation of the large reward (77 +/- 24 per sleep session) compared to earlier sessions when reward values were unequal and stable (40 +/- 9 per sleep session) ($p$ = 0.09, paired $t$-test). This observation suggests that the change in reward value is being updated and consolidated in sleep immediately following the experience. Additionally, we are exploring how awake SWR activity is modulated by changes in reward content. Together, these data aim to contribute to our understanding of how the hippocampus integrates information to support goal-directed behavior.

**Disclosures:** **B.L. Boublil:** None. **G. Tarcsay:** None. **G. Irizarry-Martinez:** None. **N. Masala:** None. **C.B. Dang:** None. **L.A. Ewell:** None. **M. Sabariego:** None.

**Poster**

**PSTR053. Learning and Memory: Hippocampal Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR053.02/UU3

**Topic:** H.08. Learning and Memory

**Title:** Bilateral coordination of hippocampal theta rhythm is important for spatial working memory in healthy and focal epileptic rodents.

**Authors: M. PASDARNAVAB**[1], L. KUECK[1], G. TARCSAY[2], *L. EWELL[4,3];
[1]Univ. of Bonn, Bonn, Germany; [2]Anat. and Neurobio., [3]Ctr. for Learning and Memory, UC Irvine, Irvine, CA; [4]UC - Irvine, Irvine, CA

**Abstract:** Several recent reports indicate that hippocampal cell assemblies comprise neurons from left and right hippocampus, which suggests a critical role for temporal coordination of activity between the two hemispheres. We observe that mice with right focal temporal lobe epilepsy (KA mice) are impaired on a spatial working memory task (KA n=13, control n=9, KA performance= 62.15±5.34%, control performance= 73.4±1.89%, p<0.05, two-way ANOVA). We hypothesized that the deficit may be driven by the dis-coordination of activity between left and right hippocampus during the task. To test this, mice were implanted with bilateral tetrode arrays and local field potentials from the CA1 cell layer were analysed. In mice with right temporal lobe epilepsy, we found a reduction in theta power (5-12 Hz) on the right side (median; 1050, IQR; 702 $uV^2$) compared to theta power on the right side of healthy control mice (median; 1608, IQR; 1013 $uV^2$). Though reduced, theta power was non-zero, allowing us to perform a coherence

analysis. We found that epileptic mice showed a reduction and bilateral theta coherence in both stem-choice (KA n=6; 0.74 ± 0.09, control n = 4; 0.81 ± 0.05, $p<0.01$, unpaired t-test) and outer arm zones of the maze (KA n=6; 0.71 ± 0.73, control n = 4; 0.78 ± 0.05). Finally, in epileptic mice, there was a significant correlation between bilateral theta coherence and working memory performance for the stem-choice zone of the maze ($R2 = 0.34$, $p<0.034$). Together these data suggest that bilateral theta coordination is important for supporting spatial working memory and is impaired in focal temporal lobe epilepsy.

**Disclosures: M. Pasdarnavab:** None. **L. Kueck:** None. **G. Tarcsay:** None. **L. Ewell:** None.

**Poster**

**PSTR053. Learning and Memory: Hippocampal Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR053.03/UU4

**Topic:** H.08. Learning and Memory

**Title:** Discimin8: a novel task to investigate the physiological mechanism of pattern separation in the dentate gyrus

**Authors: *G. TARCSAY**[1], N. MASALA[1], B. L. BOUBLIL[1], U. J. REDIC[1], L. A. EWELL[1,2]; [1]Anat. and Neurobio., [2]Ctr. for the Neurobio. of Learning and Memory, UC Irvine, Irvine, CA

**Abstract:** When encoding memories, it is often necessary to separate similar experiences to avoid interference between memories. This process is thought to be performed by the dentate gyrus (DG) of the hippocampus through a physiological process called pattern separation. However, it is unclear how the separated signals impact downstream regions with respect to task demand, such as goal-directed reward retrieval, and whether pattern separation is the driving mechanism of behavioral discrimination. To investigate these questions, we developed a novel automatized task that is performed in an octagonal-shaped arena, where each wall is equipped with a liquid reward port and with an LED cue. Mice must discriminate between adjacent LED cue pairs to obtain rewards at two distinct locations. A foraging phase is incorporated in the task to enable the exploration of how the different contexts are spatially represented in the hippocampus. We tested the task with 14 mice (8 female and 6 male). We found that females learned the task in 9+/-2 days and males in 8+/-1 days (mean+/-SEM). To assess the role of DG in the task, we lesioned bilateral dorsal DG of the expert mice (2 lesion and 2 control) and then retested them. Our preliminary data indicate an impaired performance that is recovered over days (40+/-4% on day 1 and 70+/-7% on day 4 for lesion group, 63+/-9% and 66+/-1% for control group; mean+/-SEM), suggesting that mice may use DG when it is intact, but they can effectively develop an alternative strategy to solve the task when DG is damaged. To explore how the output of the hippocampus represents the different contexts, we performed one-photon calcium imaging from large ensemble of CA1 neurons during the task using miniscope (N=1 mouse, 280 extracted spatial component). We were able to identify reward-modulated units and cells that are spatially tuned during locomotion. Most strikingly, cells with distinct spatial

activity in the two contexts were found, indicating a separate representation of the contexts. In the future we will investigate the neuronal representation of the two contexts in DG and in CA3, and the information flow between these two regions by performing electrophysiological recordings during the task.

**Disclosures: G. Tarcsay:** None. **N. Masala:** None. **B.L. Boublil:** None. **U.J. Redic:** None. **L.A. Ewell:** None.

**Poster**

**PSTR053. Learning and Memory: Hippocampal Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR053.04/UU5

**Topic:** H.08. Learning and Memory

**Title:** Longitudinal imaging of CA1 to assess dynamic hippocampal representation of value expectations

**Authors: *N. MASALA**[1], G. TARCSAY[1], B. L. BOUBLIL[1], G. IRIZARRY MARTINEZ[2,3], C. B. DANG[1], M. SABARIEGO[4], L. A. EWELL[1,3];
[1]Anat. and Neurobio., [2]Neurobio. and Behavior, [3]Ctr. for the Neurobio. of Learning and Memory, UC Irvine, Irvine, CA; [4]Mount Holyoke Col., South Hadley, MA

**Abstract:** In addition to representing spatial environments, the hippocampus represents appetitive memories and spatial reward maps, with place cells from the dorsal CA1 area that tune and increase their activity nearby reward sites. Despite the fact that acquiring and storing new memories based on reward information is crucial for the basic natural survival, little is known if these representations are plastic and how they may be updated in the face of reward unreliability. Our previous data suggest that the adaptation to reward devaluation is hippocampal dependent. On a figure 8 maze mice (female=9; male=4) learn there is a large reward (30uL sucrose) on one side and a small reward (5uL) on the other (preference to large reward is 84.23% +/- 1.58). After showing a preference for the large reward (3-4 days), such reward is devalued to 5uL for the remaining trials, while the small reward is maintained stable (preference to devalued side is 68.21% +/- 3.87). Mice that did not show significant adaptation to the reward downshift went through an additional extinction phase (preference to extinguished side is 42.5% +/- 5.95). To address how reward representation is learned in the hippocampus as well as how it might drive behavioral adaptation to reward loss, we performed calcium imaging experiments from large populations of CA1 neurons, in freely moving mice (3 mice, 410 cells). CA1 neurons showed an overrepresentation and clustering of their place fields near large reward sites (42% neurons with place field activity only near the big reward site; 13% neurons with place field activity only near the small reward site and 45% neurons with place field activity near both the big and the small reward site). Furthermore, they showed remapping after reward devaluation (26% neurons with place field activity near the downshifted reward site; 30% neurons with place field activity near the small reward site and 44% neurons with place field activity near both the shifted big and the

small reward site). Altogether these results suggest the existence of a hippocampal code that encompasses reward features like quantity or preference, which accurately predicts reward-seeking behaviors

**Disclosures:** **N. Masala:** None. **G. Tarcsay:** None. **B.L. Boublil:** None. **G. Irizarry Martinez:** None. **C.B. Dang:** None. **M. Sabariego:** None. **L.A. Ewell:** None.

**Poster**

**PSTR053. Learning and Memory: Hippocampal Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR053.05/UU6

**Topic:** D.06. Vision

**Support:** Schmidt Science Fellows, in partnership with the Rhodes Trust (S.M.L.)
WaNPRC P51OD010425
Simons Foundation SCGB 542955 (E.A.B, A.F.))
NINDS-UF1NS126485 (E.A.B, A.F.)
NIH-U19NS107609 (E.A.B., A.F., D.J.F.)

**Title:** Ultra-fast visual and spatial association learning in monkeys: a new tool to examine the hippocampal cognitive map

**Authors: *S. M. LANDI**[1,3], E. C. S. BAKOTICH[1,3,2], S. B. FERNANDEZ[1,3], K. Y. LU[1,3], V. SHIRHATTI[4], D. J. FREEDMAN[4,5], A. L. FAIRHALL[1], E. A. BUFFALO[1,3];
[1]Physiol. and Biophysics, [2]Grad. Program in Neurosci., Univ. of Washington, Seattle, WA; [3]Washington Natl. Primate Res. Ctr., Seattle, WA; [4]Neurobio., The Univ. of Chicago, Chicago, IL; [5]Univ. of Chicago Neurosci. Inst., Chicago, IL

**Abstract:** Recent studies in rodents and monkeys have demonstrated that, along with spatial locations, hippocampal neurons conjunctively code multiple aspects of behavioral task structures. These additional aspects of experience include representations of abstract value, consistent with a broader view of the nature of the hippocampal cognitive map. However, it is unclear how these representations develop during learning. To study this, we developed tasks of naturalistic free foraging in virtual reality, in which monkeys learn spatial or visual rules linked to abstract value maps. Monkeys were trained to use a joystick to navigate in an open-field virtual arena and were rewarded for sequentially harvesting rewards by colliding with visual targets. In one version of the task (feature association), the color or shape of the targets was associated with a reward value (a high, medium, or low bolus of food slurry), and the monkeys learned the feature-value associations through foraging. Monkeys were free to harvest the targets in any order, and once a target was harvested, the target disappeared from the arena. Critically, monkeys were given a limited time to harvest targets (30 s/trial); therefore, learning the feature-reward association map resulted in greater reward. In a second version of the task (spatial association), we specified a mapping between the location of the targets within the arena and

reward value, and all targets were visually identical. Given the limited foraging time, monkeys could obtain maximal reward by learning to prioritize targets in the higher value locations. Monkeys demonstrated rapid learning in both tasks, on average within three minutes for the feature association and within 10 minutes for the spatial association (significant and stable value ranking for at least five consecutive trials, Kolmogorov-Smirnov test, one-sided, $p<0.05$). As monkeys learned to choose targets in descending order of reward value, their efficiency (defined as the value of each chosen target divided by the highest value available at that time) increased and was higher than chance after only 90 seconds of foraging in the feature association task and after four minutes in the spatial association task (t-test, one-sided $p<0.05$). Unlike other behavioral tasks that can take many months for monkeys to learn, these tasks take advantage of naturalistic and intuitive foraging behavior and enable efficient and robust learning within a single behavioral session. This novel behavioral paradigm offers the opportunity to study how spatial, visual, and abstract value representations arise in the monkey hippocampus using electrophysiological approaches.

**Disclosures:** **S.M. Landi:** None. **E.C.S. Bakotich:** None. **S.B. Fernandez:** None. **K.Y. Lu:** None. **V. Shirhatti:** None. **D.J. Freedman:** None. **A.L. Fairhall:** None. **E.A. Buffalo:** None.

**Poster**

**PSTR053. Learning and Memory: Hippocampal Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR053.06/UU7

**Topic:** D.06. Vision

**Support:** NIH NINDS U19 NS107609-01

**Title:** A saccade-based foraging paradigm to study neural basis of rapid learning in non-human primates.

**Authors: *V. SHIRHATTI**[1], S. CHANG[1], S. M. LANDI[3], E. A. BUFFALO[4], D. J. FREEDMAN[2];
[1]Dept. of Neurobio., [2]Neurobio. and Computat. Neurosci., Univ. of Chicago, Chicago, IL; [3]UW Physiol. and Biophysics, [4]Physiol. and Biophysics, Univ. of Washington, Seattle, WA

**Abstract:** Rapid learning and generalization across learning experiences is a hallmark of animal behavior. However, studying this in non-human primates has so far been challenging owing to the long training times typically required for their tasks. To address this we developed a stimulus-reward association-based learning paradigm based upon a naturalistic saccade-based visual search foraging behavior. Under this saccade foraging task the monkey freely explores an array of 16 or 24 visual stimuli for 15s on each trial and harvests associated rewards by fixating a chosen stimulus for a specified duration (1.2s or 0.9s). While every harvest was rewarded, the monkey can learn to maximize reward receipt by preferentially selecting stimuli that are associated with larger reward magnitudes. Stimuli were associated with different levels of

rewards, with the stimulus features (e.g. color, shape, category) predictive of reward size varying between problem sets. The monkey successfully learnt stimulus-reward associations with stimulus sets containing hierarchies between 3 or 4 distinct color-reward associations or even 2 natural categories (e.g. faces, vehicles) within single sessions, demonstrating remarkably rapid within-session learning. Hierarchies were flexibly learnt for multiple problem sets of each type, usually within ~50-100 trials and sometimes even fewer, after which the monkey's harvest efficiency, i.e. tendency to choose the highest available reward for every harvest, was close to maximum. Learning across multiple problem sets exhibited effects of previously learnt sets and introduced systematic biases in search and harvest patterns that affected the overall speed of learning. Ongoing analysis of the monkey's saccadic behavior is focused on determining how search strategy evolves with learning. Ongoing neuronal recordings employ large scale multi-electrode arrays to examine neuronal population encoding during task performance in brain regions involved in oculomotor control - frontal eye field (FEF), lateral intraparietal area (LIP), and superior colliculus (SC) - as well as brain areas engaged in reward based learning and memory, including orbitofrontal cortex (OFC) and hippocampus. Through analysis of simultaneous recording from subsets of these brain regions, we aim to determine how rapidly learned stimulus-reward associations are transformed into effective search strategies during this naturalistic decision making task.

**Disclosures: V. Shirhatti:** None. **S. Chang:** None. **S.M. Landi:** None. **E.A. Buffalo:** None. **D.J. Freedman:** None.

**Poster**

**PSTR053. Learning and Memory: Hippocampal Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR053.07/UU8

**Topic:** H.08. Learning and Memory

**Support:** HHMI
The Cullen Foundation
HHMI via Life Sciences Research Foundation

**Title:** Memory encoding, storage, and retrieval in recurrent neural networks with behavioral timescale synaptic plasticity

**Authors: *J. J. BRIGUGLIO**[1], Y. LI[2], J. C. MAGEE[2], S. ROMANI[1];
[1]Janelia Res. Campus, Ashburn, VA; [2]Baylor, Houston, TX

**Abstract:** Rapid storage of new information, an essential cognitive process, is thought to be facilitated by alterations in synaptic strength within neural circuits. The hippocampus, specifically its CA3 subregion, plays a critical role in this process, rapidly forming activity patterns that represent spatial, temporal, and additional variables necessary for episodic memory. Existing models and theories for online one-shot learning predominantly focus on Hebbian-like

synaptic plasticity, which requires complex synapses and unrealistic, non-interfering, uncorrelated activity patterns. Here we show that temporally symmetric behavioral timescale synaptic plasticity (BTSP), a plasticity rule found in the CA3 subregion, enables pattern decorrelation within recurrent networks, thus optimizing memory storage and retrieval. Our findings suggest a novel synaptic mechanism for pattern separation and completion in the hippocampus, providing a new perspective into the role of the hippocampus in episodic memory and one-shot learning.

**Disclosures:** **J.J. Briguglio:** None. **Y. Li:** None. **J.C. Magee:** None. **S. Romani:** None.

**Poster**

**PSTR053. Learning and Memory: Hippocampal Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR053.08/UU9

**Topic:** H.08. Learning and Memory

**Support:** HHMI
Cullen Foundation
Life Sciences Research Foundation

**Title:** Mechanisms of memory storage and retrieval in hippocampal area CA3

**Authors: *Y. LI**[1], J. BRIGUGLIO[2], S. ROMANI[3], J. C. MAGEE[4];
[1]Neurosci., Howard Hughes Med. Institute, Baylor Col. of Med., Houston, TX; [2]HHMI, Janelia Res. Campus, Ashburn, VA; [3]HHMI Janelia Res. Campus, HHMI Janelia Res. Campus, Ashburn, VA; [4]HHMI, BAton Rouge, LA

**Abstract:** Hippocampal area CA3 is thought to play a central role in memory formation and retrieval. Although various network mechanisms have been hypothesized to mediate these computations, direct evidence is lacking. Using intracellular membrane potential recordings from CA3 neurons and optogenetic manipulations in behaving mice we found that place field activity is produced by a symmetric form of Behavioral Timescale Synaptic Plasticity (BTSP) at recurrent synaptic connections among CA3 principal neurons but not at synapses from the dentate gyrus (DG). Additional manipulations revealed that excitatory input from the entorhinal cortex (EC) but not DG was required to update place cell activity based on the animal's movement. These data were captured by a computational model that used BTSP and an external updating input to produce attractor dynamics under online learning conditions. Additional theoretical results demonstrate the enhanced memory storage capacity of such networks, particularly in the face of correlated input patterns. The evidence sheds light on the cellular and circuit mechanisms of learning and memory formation in the hippocampus.

**Disclosures:** **Y. Li:** None. **J. Briguglio:** None. **S. Romani:** None. **J.C. Magee:** None.

**Poster**

**PSTR053. Learning and Memory: Hippocampal Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR053.09/UU10

**Topic:** H.08. Learning and Memory

**Support:** HHMI

**Title:** Experience-dependent flexible place cell representations in the hippocampal CA1

**Authors: *K. QIAN**[1], Y. LI[2], J. C. MAGEE[3];
[1]Neurosci., Baylor Col. of Med., HOUSTON, TX; [2]1250 Moursund St, Suit 950, Howard Hughes Med. Inst., houston, TX; [3]HHMI, BAton Rouge, LA

**Abstract:** The place cells (PCs) in the hippocampal CA1 are known for using both self-centric (egocentric) and world-centric (allocentric) reference frames to support a cognitive map. How these two reference frames are combined to drive PC activity, and the role of experience in this process, remain poorly understood. Here we longitudinally recorded CA1 PCs while mice performed a spatial learning task on a linear treadmill. In a familiar environment, the CA1 representation comprised of both allocentric PCs and egocentric PCs. The distinct spatial preferences and the inverse correlation between the fraction of each PC type suggested that they are formed competitively. However, the introduction of a novel environment altered the pre-established hybrid map into a homogeneous egocentric map. Besides, individual allocentric PCs adaptively transformed into egocentric PCs in a novel environment. Finally, our results revealed that behavioral time scale synaptic plasticity (BTSP) preferentially stabilized pre-formed place fields for allocentric PCs while abruptly introduced new place fields for egocentric PCs after the reward switch. The results suggest that experience binds the CA1 PC representation flexibly to allocentric and egocentric reference frames through BTSP for behavioral adaptations.

**Disclosures: K. Qian:** None. **Y. Li:** None. **J.C. Magee:** None.

**Poster**

**PSTR053. Learning and Memory: Hippocampal Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR053.10/UU11

**Topic:** D.06. Vision

**Title:** Altered visual exploration following repeated viewing in a natural scene recall task

**Authors: *P. N. CHAKRAVARTHULA**[1], J. SUFFRIDGE[2], X. LI[3], S. WANG[4];
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**Abstract:** Humans have a foveated visual system that can sample high-fidelity information from only one location at any given time. When tasked with recalling previously encountered information, the visual system faces a unique challenge: to select information that is most likely to be consistent with the information sampled during encoding. How does this process occur? To address this question, we recorded the eye movements of 20 healthy observers while they participated in a natural scene recall task with 200 unique scenes presented across two sessions. Each scene appeared once, twice, or three times, with a duration of 3 seconds per presentation. Observers were free to move their eyes to examine the scenes. At the end of each trial, they reported whether they had seen the image or not, along with rating their confidence on a six-point scale. First, we found that the observers achieved a high accuracy (average percent correct 95.6%) on the task. Second, observers explored a significantly higher fraction of the scene during the first viewing compared to the second and third viewings. Moreover, from the second to the seventh fixation, repeated viewing of the scene was associated with significantly increased fixation durations. Thirdly, we employed computational modeling to characterize the role of stimulus features (at the pixel, object, and semantic levels), visual salience, and image memorability in determining fixation locations and durations. Although we did not find any significant differences in features driving fixation locations with repetitions, we found that repeated viewing had a significant interaction effect with the local memorability at the fixated locations. This interaction revealed that memorable locations were fixated longer only when images were repeated. In summary, our results indicate that the visual system employs a sophisticated information selection strategy that balances visual exploration and the sampling of more memorable regions that may support recall in a scene memory task.

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**Poster**

**PSTR053. Learning and Memory: Hippocampal Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR053.11/UU12

**Topic:** H.08. Learning and Memory

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R01 MH120162
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Mount Sinai Distinguished Scholar Award
Friedman Brain Institute Award
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**Title:** Aversive experience drives offline ensemble reactivation to link memories across days

**Authors: *Y. ZAKI**[1], Z. PENNINGTON[3], S. CARRILLO SEGURA[5], D. MORALES-RODRIGUEZ[6], T. FRANCISCO[3], A. LABANCA[3], Z. DONG[2], Z. CHRISTENSON WICK[2], A. SILVA[7], T. SHUMAN[8], A. FENTON[9], K. RAJAN[4], D. CAI[10];
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**Abstract:** Memories are encoded in neural ensembles during learning and stabilized by post-learning reactivation. Integrating recent experiences into existing memories ensures that memories contain the most recently available information, but how neural ensembles accomplish this critical process remains unknown. Here we show that in mice, a strong aversive experience drives the offline ensemble reactivation of not only the recent aversive memory but also a neutral memory formed two days prior, spreading the fear from the recent aversive memory to the previous neutral memory. We find that fear specifically spreads retrospectively, but not prospectively, to neutral memories across days. Consistent with prior studies, we find reactivation of the recent aversive memory ensemble during the offline period following learning. However, a strong aversive experience also increases co-reactivation of the aversive and neutral memory ensembles during the offline period. Surprisingly, we find that this ensemble co-reactivation occurs during wake rather than during sleep. Finally, inhibiting hippocampal reactivation during this offline period abolishes the spread of fear from the aversive experience to the neutral memory. Taken together, these results demonstrate that strong aversive experience can drive retrospective memory integration through the offline co-reactivation of recent memory ensembles with memory ensembles formed days prior, providing a neural mechanism by which memories can be integrated across days. Ultimately, these results lend insight into how the brain draws inferences about causal associations across long timescales.

**Disclosures: Y. Zaki:** None. **Z. Pennington:** None. **S. Carrillo Segura:** None. **D. Morales-Rodriguez:** None. **T. Francisco:** None. **A. LaBanca:** None. **Z. Dong:** None. **Z. Christenson Wick:** None. **A. Silva:** None. **T. Shuman:** None. **A. Fenton:** None. **K. Rajan:** None. **D. Cai:** None.

**Poster**

**PSTR053. Learning and Memory: Hippocampal Physiology**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR053.12/UU13

**Topic:** H.08. Learning and Memory

**Support:** F32AG067640
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**Title:** Decreasing neuronal co-activity supports memory updating.

**Authors: *A. BAGGETTA**[1], W. MAU[2], M. J. TILLEY[3], M. MILLER[3], Z. DONG[2], B. M. SWEIS[2], D. MORALES-RODRIGUEZ[2], Z. T. PENNINGTON[2], T. R. FRANCISCO[2], D. J. FREEDMAN[3], M. BAXTER[4,2], T. SHUMAN[2], D. J. CAI[2];
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**Abstract:** Memory updating is critical in dynamic environments because updating memories with new information promotes versatility. However, little is known about how memories are updated with new information. To study how neuronal ensembles might support memory updating, we used Miniscope calcium imaging in a memory updating task to measure hippocampal ensemble dynamics when mice switched navigational goals. Distinct neuronal ensembles were identified by their coordinated activity, and during an updating test we observed that a fraction of the total detected ensembles decreased their coordinated activity across time. The proportion of these “fading” ensembles correlated with performance during the updating test, and interestingly middle-aged mice, who were impaired during the updating test, had fewer fading ensembles. While this is indicative of fading ensembles aiding performance, we turned to modeling the system to precisely determine the function of these ensembles. We developed a neural network with one hidden layer to perform the same water reward port task using the reinforcement learning algorithm PPO. We identified fading ensembles in the model during the updating test using the same analysis and then “ran the model back in time” and turned them off during the updating test. We observed that turning off fading ensembles alters model performance, suggesting that fading ensembles support memory updating. Future work will aim to characterize whether there is also an emergence of new ensembles during the updating test to represent the integration of new information.

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**Poster**

**PSTR053. Learning and Memory: Hippocampal Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR053.13/UU14

**Topic:** H.08. Learning and Memory

**Support:** NSF CAREER IOS-1844935
NIH R01 MH123466

**Title:** Update in the hippocampal representation reveals neural signature of retrospective memory-linking

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**Abstract:** How are aversive experiences linked with past memories to influence future behavior? Many studies have focused on how individual memories are stabilized in the brain, but relatively little is known about how the brain dynamically updates and integrates new memories with past experiences. Integrating recent experiences into previously learned memories is critical so that memories contain the most recent available information. We found that increasing the aversiveness of an experience leads to transfer of fear from the aversive context to a neutral memory which was formed several days prior. Such memory linking across distinct contexts implies a representational change in which two ensemble activity patterns become more similar as a result of the aversive experience. Previous studies have suggested that a shared neural ensemble, co-active between two contexts, can promote similar representations and thus facilitate linkage of two memories. However, it is unclear whether a change in which neurons participate in the shared ensemble is sufficient, or if changes in firing patterns also contribute. To address this question, we first quantified the firing rate similarity across the entire ensemble of dorsal CA1 neurons between the neutral and aversive contexts. Following aversive experience, we observed a significant increase in ensemble similarity in those mice that exhibited fear transfer to the previously neutral context. Furthermore, we found that the overlapping ensemble between the two memories underwent a greater representational drift in the neutral context specifically in fear-transferred mice, and this direction of drift was not random but instead reflected an update in neural activity space towards the aversive context. These findings reveal a neural mechanism of memory linkage from a representational similarity perspective: fear memory generalization across contexts involves not only a change in which neurons participate (overlap) but also involves a representational shift in the ensemble activity pattern of overlapping neurons, where the previously neutral context becomes more similar to the aversive context.

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**Poster**

**PSTR053. Learning and Memory: Hippocampal Physiology**

**Location:** WCC Halls A-C

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**Topic:** H.08. Learning and Memory

**Support:** NIH BRAIN Initiative grant U19NS104590

**Title:** Neural representations arising during the application of an abstract rule

**Authors: *A. TSAO**[1,2], M. J. SCHNITZER[1,2,3,4];
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**Abstract:** A central way in which abstraction contributes to cognition is by allowing information learnt from specific instances to be flexibly and efficiently applied to general and novel situations. The neural mechanisms underlying this flexibility remain poorly understood. To study how the brain learns and applies generalized rules, we trained rats to perform a learning set task comprising a series of odor discrimination problems. Each problem is conducted on a continuous T-maze and involves two unique odors; on each trial, we presented rats with one of the two odors, chosen randomly and indicating whether to turn left or right to receive a reward. This task has a simple abstract structure such that a win-stay/lose-shift strategy yields perfect performance after the initial trial of each problem reveals the mapping between the odor pair and turning directions. In rats trained on tens of problems, we found evidence for learning of the abstract rule. Specifically, rats' performances on the first trial of the second odor encountered in each problem were significantly above chance levels, showing they had inferred the underlying task structure. To examine the neural basis for this, we used a head-mounted miniature microscope to perform longitudinal imaging studies of the $Ca^{2+}$ dynamics of hundreds of individual CA1 hippocampal pyramidal cells as rats acquired and applied the abstract rule. The data revealed two subsets of pyramidal cells whose activity may relate to the abstract task structure. About 9% of odor-encoding cells responded across multiple problems to different odors that all signaled the same turning direction; these cells seem to encode odor identity as it relates to the task structure. About 12% of place cells with place fields on the central stem of the T-maze but before the choice point exhibited rate-remapping that was predictive of the rat's upcoming choice across multiple problems; these cells seem to encode the animal's response on each trial. Both groups of cells emerged during the intermediate stage of learning, when rats were familiar with the task but not yet reliably using the abstract rule. Late in this stage of learning, a separate set of odor-encoding cells with long response latencies (>700 ms after odor onset) emerged whose activity arose and stabilized on the first few trials of a problem and was specific to individual problems. These cells appear to provide a temporal link between the abstract representations of odor identity and the motor response, and thus might reflect the mapping of specific odors from a given problem onto the abstract rule of the task. In our ongoing work, we are exploring the mechanisms by which this mapping occurs.

**Disclosures: A. Tsao:** None. **M.J. Schnitzer:** Other; MJS was a co-founder of Inscopix Inc, the manufacturer of the miniature integrated microscope; however, this financial interest was fully removed partway through our study.

**Poster**

**PSTR053. Learning and Memory: Hippocampal Physiology**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR053.15/UU16

**Topic:** H.08. Learning and Memory

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GINOP_PLUSZ-2.1.1-21-2022-00143
PM/20453-15/2020

**Title:** Sharp-wave ripple doublets induce complex dendritic spikes in parvalbumin interneurons in vivo

**Authors: *S.-J. LINDA**[1], B. CHIOVINI[2], G. JUHASZ[4], D. PALFI[4], Z. MEZRICZKY[4], Z. SZADAI[1], G. KATONA[4], K. ÓCSAI[4], A. MIHÁLY[4], B. MARTINECZ[3], A. DENES[3], Á. SZEPESI[2], G. SZALAY[2], B. ROSKA[5], B. ROZSA[2];
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**Abstract:** Neuronal plasticity has been shown to be causally linked to coincidence detection through dendritic spikes (dSpikes). We demonstrate the existence of SPW-R-associated, branch-specific, local dSpikes and their computational role in hippocampal PV+ interneurons in awake animals. To measure the entire dendritic arbour of long thin dendrites during SPW-Rs, we used fast 3D acousto-optical imaging through an eccentric deep-brain adapter and ipsilateral local field potential. Our approach revealed the existence of SPW-R-dSpikes in vivo. These were initiated in a minority of dendrites in distal dendritic regions from multiple hot spots and, following a time delay, they propagated towards the soma and to the more distal part of the dendrite. In contrast to our previous in vitro work, the amplitude of the SPW-R-dSpike had a pronounced amplitude increase at the critical spatial threshold (~150 µm from the soma) in distant dendritic segments. A novel supralinear dendritic summation emerged during SPW-R doublets when two successive SPW-R events coincide within a short temporal window (~150 ms), e.g., during more complex association tasks, and generated large dSpikes. Our results indicate that these doublet-associated dSpikes can work as a dendritic-level temporal and spatial coincidence detector for the two input assemblies generated by the two events of SPW-R doublets in awake mice. Moreover, we were able to investigate doublets which never occurred under in vitro conditions and described an about 2.5-3-fold increase in the amplitude of the

dSpike during doublets which revealed a novel, dendritic computational level for coincidence detection.

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**Poster**

**PSTR053. Learning and Memory: Hippocampal Physiology**

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**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR053.16/UU17

**Topic:** H.08. Learning and Memory

**Support:** P50 MH109429
R01 DC012947

**Title:** Phase coding across the saccade-fixation cycle in human hippocampus

**Authors: *M. LESZCZYNSKI**[1], E. ESPINAL[2], E. SMITH[3], C. SCHEVON[4], S. SETH[5], C. E. SCHROEDER[6];
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**Abstract:** Natural vision is an active sensing process that entails moving the eyes multiple times per second to sample the environment. Nonetheless vision is often studied using passive viewing with eye position held constant. Using closed-loop eye-tracking, with saccade-contingent stimulation and simultaneous intracranial recordings from human Medial Temporal Lobe (hippocampus and amygdala), we found that passive viewing does not capture critical components of natural vision. Saccades elicit a predictive phase reset, which aligns neural ensemble excitability oscillations to enhance response to visual input. Saccades also modulate network connectivity. Finally, visual information appears to be phase-coded across the saccade-fixation cycle. The saccade-fixation cycle thus emerges as a fundamental unit of information sampling, organizing specific neural operations and information coding. These findings underscore the importance of accounting for the active nature of vision to fully understand the neural mechanisms of visual information processing.

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**Poster**

**PSTR053. Learning and Memory: Hippocampal Physiology**

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**Topic:** H.08. Learning and Memory

**Support:** NSF DGE-1839285
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**Title:** Ca1 local field potential activity contains sufficient information to decode trial-specific non-spatial information

**Authors: *K. W. COOPER**[1], W. ZHOU[2], B. SHAHBABA[2], N. J. FORTIN[1];
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**Abstract:** The hippocampus is known to play a critical role in the memory of sequences of events. To shed light on the hippocampal mechanisms supporting this capacity, we recorded neural activity in dorsal CA1 while rats performed a non-spatial odor sequence memory task. In this task, rats receive multiple presentations of a given sequence of odors in the same port and, for each odor, are required to correctly determine whether it was presented in sequence (e.g., AB<u>C</u>⋯) or out of sequence (e.g., AB<u>D</u>⋯). In our previous work, we showed that information about trial content, such as the identity of the odor presented and whether it was presented in or out of sequence, could be accurately decoded from the ensemble spiking activity. Here we tested the hypothesis that information about trial content can also be decoded from the local field potential (LFP) activity alone, and that the content varies across the proximal-distal axis of dorsal CA1. To achieve this, we leveraged recent developments in graph neural network models to identify patterns in the LFP activity across electrodes that significantly predicted trial-specific information (in this case whether the odor was presented in or out of sequence). We found that significant nodes (tetrodes) and significant edges (relationships between tetrodes) clustered primarily in the distal region of the hippocampal axis, and this pattern of significance could be detected before the animals' decision. These findings suggest that CA1 LFP activity contains sufficient information to decode non-spatial memory-guided decisions, and that such representations are more pronounced in the segment of CA1 more strongly associated with the lateral entorhinal cortex.

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**Poster**

**PSTR053. Learning and Memory: Hippocampal Physiology**

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**Topic:** H.08. Learning and Memory

**Support:** NIMH (R01 MH113071)
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Dr. Miriam and Sheldon G. Adelson Medical Research Foundation

**Title:** Compartmentalized dendritic plasticity in the retrosplenial cortex integrates memories across time

**Authors: *M. SEHGAL**[1], D. ALMEIDA[1], G. I. KASTELLAKIS[2], S. KIM[3], J. LEE[4], S. HUANG[1], A. LAVI[1], G. FERNANDES[1], S. MARTIN[1], I. D. MEJIA[1], A. PEKCAN[1], M. WU[1], W. D. HEO[4], P. POIRAZI[5], J. T. TRACHTENBERG[6], A. J. SILVA[7];
[1]Univ. of California Los Angeles, Los Angeles, CA; [2]IMBB/FORTH, IMBB/FORTH, Heraklion, Greece; [3]IBS/KAIST, IBS/KAIST, DAEJEON, Korea, Republic of; [4]KAIST, KAIST, Daejeon, Korea, Republic of; [5]IMBB-FORTH, IMBB-FORTH, Heraklion, Crete, Greece; [6]UCLA, UCLA, Los Angeles, CA; [7]Departments of Neurobiology, Psychiatry & Biobehavioral Sciences, and Psychology, UCLA, Westowood, CA

**Abstract:** Events occurring close in time are often linked in memory, providing an episodic timeline and a framework for those memories. Recent studies suggest that memories acquired close in time are encoded by overlapping neuronal ensembles, but the role of dendritic plasticity mechanisms in linking memories is unknown. Using activity-dependent labeling and manipulation approaches, longitudinal one- and two-photon imaging of somatic and dendritic compartments, and computational modeling, we show that memory linking is not only dependent on ensemble overlap in the retrosplenial cortex, but also on branch-specific dendritic allocation mechanisms. The same dendritic segments are preferentially activated by two linked memories, and spine clusters added after each of the two linked memories are allocated to the same dendritic segments. Our results demonstrate a causal mechanistic role for dendritic plasticity in memory integration, and reveal a novel set of rules that govern how linked and independent memories are allocated to dendritic compartments.

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**Poster**

**PSTR054. Head Direction, View, and Spatially Modulated Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR054.01/UU20

**Topic:** H.09. Spatial Navigation

**Title:** Coding of position by action in the medial entorhinal cortex of flying bats

**Authors: *G. GINOSAR**[1], D. MCNAMEE[3], L. LAS[2], N. ULANOVSKY[1];
[2]Dept. of Neurobio., [1]Weizmann Inst. of Sci., Rehovot, Israel; [3]Champalimaud Ctr. for the Unknown, Lisbon, Portugal

**Abstract:** The medial entorhinal cortex (MEC) contains a diversity of spatially-tuned cells. These cells are typically recorded and characterized as animals randomly forage for food. However, real-world behaviors include a variety of actions beyond random foraging, and it is unclear to what degree is spatial coding affected by the actions the animal performs. Here we recorded from the MEC of flying bats as they engaged either in random foraging flights, or in one of two distinct actions: takeoff and landing. Bats flew in a large flight-room in which 6-11 identical rest-platforms were placed at various locations. The area around each platform allowed us to investigate the neural code in the same spatial location but under different actions: random-foraging fly-bys next to the platform vs. landing on the platform vs. takeoff from the platform. We found that a substantial fraction of cells in the deep layers of MEC (but not superficial layers) fired at specific locations - i.e. at the vicinity of specific platforms - only under specific actions. These cells fired near the platform either when the bat performed landing or takeoff from the platform, but not when it flew through the same location in random foraging without taking a distinct action. Thus, these MEC neurons encoded position by action. We show that in the reinforcement learning framework, while grid cells provide a low-dimensional basis of space under random foraging, a signal encoding position by action, as found here, acts as the low-dimensional basis of spaces under directed action.

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**Poster**

**PSTR054. Head Direction, View, and Spatially Modulated Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR054.02/UU21

**Topic:** H.09. Spatial Navigation

**Title:** Model of hippocampal episodic memory unified with and enabled by prestructured spatial representations

**Authors:** S. SHARMA[1], ***S. CHANDRA**[3], I. R. FIETE[2];
[1]Brain and Cognitive Sci., MIT, CAMBRIDGE, MA; [2]Ctr. for Learning and Memory, MIT, Cambridge, MA; [3]Massachussetts Inst. of Technol., Cambridge, MA

**Abstract:** Hippocampal circuits in the brain participate in two distinct cognitive functions: building spatial maps for navigation and storing sequential episodic memories. The dual role of this structure in general episodic memory and spatial memory functions is an enduring enigma.

Here we present a neocortical-entorhinal-hippocampal network model that exhibits high-capacity spatial and non-spatial memory with graceful degradation, using biologically plausible one-shot learning. The model factorizes content storage from the dynamics of generating high-capacity error-correcting stable states. Next, we show that pre-structured spatial representations are an essential feature for constructing episodic memory: unlike existing episodic memory models, they enable high-capacity memorization of sequences by abstracting the chaining problem into one of learning transitions within a rigid low-dimensional grid cell scaffold. Remarkably, this model also recapitulates and explains a wealth of hippocampal phenomenology, such as the observation of splitter cells, directional grid and place cells, and context and route dependent cells.Finally, we show that previously learned spatial sequences in the form of location-landmark associations can themselves be re-usably leveraged as robust scaffolds for association with neocortical inputs for even-larger capacity and more-accurate one-shot memory, providing the first circuit model of ``memory palaces'' that enable the striking feats of memory athletes.

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**Poster**

**PSTR054. Head Direction, View, and Spatially Modulated Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR054.03/UU22

**Topic:** H.09. Spatial Navigation

**Title:** Systems Neuroscience of Head Direction Cells in the naturally behaving Marmoset Monkey

**Authors:** F. LANZARINI, N. EL MAHMOUDI, F. ZIAIE NEZHAD, D. SURENDRAN, C. ILLING, ***J. LAURENS**;
Ernst Strüngmann Inst. for Neurosci., Frankfurt am Main, Germany

**Abstract:** During their daily activities, non-human primates frequently need to orient in their environment in order to locate themselves, remember relevant sites, and plan routes. This ability depends on a variety of neurons, amongst which Head direction cells (HDC) that encode allocentric head orientation, akin to a “neuronal compass”.
To date, HDC have mostly been studied in rodents, typically single individuals foraging in simple environments. This fails to capture some key aspects of primate behavior: primates rely more on their visual system than rodents, have higher cognitive abilities, exhibit a wide range of social behaviors, and move in 3D.
In view of this, we have designed a freely-moving setup for marmosets (Callithrix jacchus), based on a large enclosure (4 m3) densely filled with assorted enrichments that reproduce the natural arboreal substrate. We use a retroreflective markers-based motion capture system with 24 cameras to robustly track multiple animals’ head movements simultaneously, and we plan to use data loggers to record up to 64 channels of neuronal data for up to three hours.
Six marmosets have been trained to enter the setup by pairs. We designed training techniques to

establish a consistent and stress-free routine across experimental sessions. Marmosets spend up to 3 hours per session in the enclosure, in pairs, and exhibit a large range of natural behaviors. They can be trained to visit remote-controlled reward dispensers. This methodology will pave the way for ethologically-relevant investigation of the navigation system.

**Disclosures: F. Lanzarini:** None. **N. El Mahmoudi:** None. **F. Ziaie Nezhad:** None. **D. Surendran:** None. **C. Illing:** None. **J. Laurens:** None.

**Poster**

**PSTR054. Head Direction, View, and Spatially Modulated Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR054.04/UU23

**Topic:** H.09. Spatial Navigation

**Support:** NIMH 1ZIAMH002881
NIMH ZICMH002952

**Title:** Working memory and reward increase the accuracy of encoding animal location in the medial prefrontal cortex

**Authors: *X. MA**, C. ZHENG, Y. CHEN, F. PEREIRA, Z. LI;
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**Abstract:** The ability to perceive spatial environments and locate oneself during navigation is crucial for the survival of animals. The entorhinal cortex and hippocampus are the most studied areas for spatial representation during navigation behavior. Mounting evidence also suggests a role of the medial prefrontal cortex (mPFC) in spatially related behaviors, such as goal-directed actions, path planning, and strategy switching in spatial working memory tasks. However, the properties of mPFC spatial encoding and how it is influenced by animal behavior are poorly defined. Here, we train the mice to perform three tasks differing in working memory and reward-seeking: a delayed non-match to sample (DNMTP) task, a passive alternation (PA) task, and a free-running (FR) task. Working memory is required for the animals to perform in the DNMTP task, while it is not required in the PA or FR task. Rewards are provided in the DNMTP and PA tasks but not in the FR task. Single-unit recordings in the mPFC show that while individual mPFC neurons exhibit spatially selective firing in mean firing rate maps during the three tasks, they do not reliably represent the animal location from trial to trial. Despite the low spatial information carried by single neurons, with a Bayesian decoder, we can decode the animal location from population neuron spiking activities. These results suggest that the mPFC encodes the animal location at the population level as opposed to the single-cell level. Notably, the spatial information index of single neurons, as well as the coding accuracy of animal locations by neural populations is highest in the DNMTP task, lower in the PA task, and lowest in the FR task. These findings indicate that both working memory and reward-seeking increase the accuracy of

location coding at the mPFC. This study reveals an approach by which the mPFC encodes spatial positions and how it is impacted by behavioral variables.

**Disclosures:** **X. Ma:** None. **C. Zheng:** None. **Y. Chen:** None. **F. Pereira:** None. **Z. Li:** None.

**Poster**

**PSTR054. Head Direction, View, and Spatially Modulated Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR054.05/UU24

**Topic:** H.09. Spatial Navigation

**Support:** ANR
Aix Marseille University
Laboratory of Cognitive Neuroscience

**Title:** Retrosplenial cortex activity represents both local and global space

**Authors: *C. LAURENT**[1,2], F. SARGOLINI[2], P.-Y. JACOB[2];
[2]Lab. de Neurosciences Cognitives UMR7291, [1]Aix-Marseille Univ., Marseille, France

**Abstract:** Every day, we navigate between connected rooms to reach goals. This requires a mental map of the environment based on two reference frames: one for each room (local reference frame) and one including spatial relationships between all connected rooms (global reference frame). Recent studies in rodents suggest that the retrosplenial cortex (RSC) may simultaneously code for both reference frames. Indeed, single unit recording in rats exploring two symmetrical connected rooms show that RSC contains two distinct functional cell populations: head direction cells (HDC) firing when the animal faces a particular direction regardless the number of rooms thus providing a global directional signal; and bi-directional cells (BDC) displaying distinct directions each specific for one room, suggesting that their activity is anchored to a local space. Here we tested whether these two populations of cells still provide global and local directional signals in environments with two or four visually different connected rooms. We found that HDC firing direction is maintained regardless of the number of rooms. Furthermore, BDC fire in two directions when rodents navigate between two different connected rooms and tend to fire in four directions in four connected rooms. We also observed that non-directional RSC cells show identical spatial activity but reversed between connected rooms, similarly to BDC. This indicates that coding of local and global spaces is not limited to HDC and BDC. Altogether, these results confirm that RSC may form global and local reference frames necessary for the construction of a cognitive map which allows navigation in complex environments.

**Disclosures:** **C. Laurent:** None. **F. Sargolini:** None. **P. Jacob:** None.

**Poster**

**PSTR054. Head Direction, View, and Spatially Modulated Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR054.06/UU25

**Topic:** H.09. Spatial Navigation

**Support:** MPG to Gilles Laurent

**Title:** Lizard Septum from spatial transcriptomics to spatial representation

**Authors: *S. WEISS**[1,2], T. LAI[3,4], D. HAIN[2,5], M. GALLEGO FLORES[6,2], G. J. LAURENT[2]; [1]NSK, Max Planck Inst., Frankfurt Am Main, Germany; [2]Max Planck Inst. For Brain Res., Frankfurt/Main, Germany; [3]Inst. for Physiol., Johannes Gutenberg Univ. Mainz, Mainz, Germany; [4]Frankfurt Inst. for Advanced Studies, [5]Fac. of Biol. Sci., Goethe Univ. Frankfurt, Frankfurt am Main, Germany; [6]Achucarro Basque Ctr. for Neurosci., Leioa, Spain

**Abstract:** The reptile forebrain shares a layered cortical architecture with mammals, as presumably did their common ancestor. Indeed, the reptilian dorsomedial and medial cortices are transcriptomically similar to the mammalian hippocampal CA fields and DG respectively. Our aim is to characterize the conserved and divergent molecular, structural and functional features of the limbic system in amniotes. We present here data on the septum, a key region of this system. The septum occupies 12.1% of the forebrain's subpallial volume (µCT scans of Bearded dragon lizards *Pogona vitticeps*, at 8.42µm resolution). Its function in reptiles, and how it compares with that in mammals, however, are not well understood. We thus set out to characterize the anatomy, architecture, connectivity, gene-expression patterns and electrophysiological features of the Pogona septum. We used data from scRNAseq (Tosches et al., 2018; Hain, Gallego-Flores et al., 2022) to identify septal sub-clusters. Genes extracted from those clusters were used in multiplexed HCR RNA-FISH and spatial transcriptomics to establish the spatial distribution of cell clusters across the septum. Next, we used viral (AAV2/rg, AAV2/9) and tracer injections (BDA, Fluorogold, Neurobiotin) to map the connectivity of the septal subdivisions. Finally, we carried out chornic recordings from the septum using Neuropixels probes. During sleep, sharp-wave ripples (SWR) lagged behind those recorded in the claustrum but preceded those in hippocampus. In freely moving lizards (open-field arena, n=6 males120-300 grams), activity in isolated single units was correlated with some aspects of the behavior (measured with a GLM procedure). We found septal cells that displayed selectivity for speed, head-direction, position and, surprisingly, egocentric boundaries. This stands in contrast to the allocentric nature of septum reported so far in mammals. In summary, we applied modern molecular and electrophysiological tools to conduct an exhaustive exploration of the lizard septum, yielding insights into the potential evolution of spatial representation systems among amniotes.

**Disclosures: S. Weiss:** None. **T. Lai:** None. **D. Hain:** None. **M. Gallego Flores:** None. **G.J. Laurent:** None.

**Poster**

**PSTR054. Head Direction, View, and Spatially Modulated Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR054.07/UU26

**Topic:** H.09. Spatial Navigation

**Title:** Characterization of inhibitory interneuron dynamics during remapping in medial entorhinal cortex

**Authors: *J. SHI**[1], J. G. HEYS[2];
[1]Univ. of Utah, salt lake city, UT; [2]Neurobio. and Anat., Univ. of Utah, Salt Lake City, UT

**Abstract:** The medial entorhinal cortex (MEC) is critical for navigation and spatial memory. MEC contains two distinct spatial-coding cell types known as the 'grid cells' and the 'non-grid spatial cells'. In an open environment, grid cells fire regularly at specific locations arranged in a hexagonal 'grid' pattern, while non-grid spatial cells fire selectively at one or two locations and do not display spatial periodicity. Interestingly, when an animal navigates across distinct environments, grid cell populations coherently translate their periodic firing fields to 'realign' with the novel environment, while non-grid spatial cells randomly rearrange firing fields independent of each other. It is unclear what circuit mechanisms lead to their distinct responses to novel environments. Previous work showed that inhibition of MEC parvalbumin (PV)-expressing interneurons disrupted the spatial selectivity of grid cells, but not non-grid spatial cells. Conversely, inhibition of somatostatin (SOM)-expressing interneurons exclusively disrupted the spatial selectivity of non-grid spatial cells but not grid cells. Building on these findings, we propose that MEC contains two parallel circuits: 1) a structured network consists of PV+ interneurons and grid cells with rigid synaptic connections; 2) a more flexible network consists of SOM+ interneurons and non-grid spatial cells that is well suited to mediate experience dependent plasticity. Previously using 2-photon Ca2+ imaging combined with transgenic mouse strains, we specifically recorded the activity of PV+ and SOM+ interneuron types while the mouse was navigating through different virtual environments. We found that 1) the mean population activity of PV+ interneurons is elevated during the ~10 mins interval navigating in novel environments; 2) the mean population activity of SOM+ interneurons did not change but individual cells show heterogeneous response to novel environments. To further investigate whether activity changes of PV+ and SOM+ interneurons are required for remapping in MEC, we are using the DREADDs system to manipulate the activity of either PV+ or SOM+ interneurons while the mouse was exposed to novel virtual environments. We hypothesize that 1) inhibiting PV+ interneurons will disrupt the spatial selectivity and stability of grid cells in novel environments and 2) inhibiting SOM+ interneurons will make the spatial fields of non-grid spatial cells to emerge earlier in novel environment but become less stable over time. Together, these findings will help uncover the MEC circuit mechanisms responsible for navigation in novel environments.

**Disclosures: J. shi:** None. **J.G. Heys:** None.

**Poster**

**PSTR054. Head Direction, View, and Spatially Modulated Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR054.08/UU27

**Topic:** H.09. Spatial Navigation

**Support:** THE ISRAEL SCIENCE FOUNDATION—FIRST Program (Grant no. 555/19),
Human Frontiers Science Foundation Grant RGP0016/2019

**Title:** Representation of Hydrostatic Pressure in the Brain of Freely Navigating Goldfish

**Authors:** L. COHEN[1], E. VINEPINSKY[2], O. DONCHIN[3], ***R. SEGEV**[4];
[1]Ben-Gurion Univ. of the Negev, Beer Sheva, Israel; [2]Inst. de Biologie de l'École Normale Supérieure, Paris, France; [3]Ben Gurion Univ., Ben Gurion Univ., Be'er Sheva, Israel; [4]Ben Gurion Univ. of the Negev, Beer Sheva, Israel

**Abstract:** Navigation is a high order cognitive ability which is crucial for the survival of fish and almost all animals. This makes it an excellent model system for understanding the development of cognitive abilities across all vertebrate classes. This study explored how depth is represented in the brains of fish, the largest group of vertebrates. Fish navigate in an aquatic environment where the density of water is about 800 times greater than air. This makes fish navigation fundamentally different from surface-dwelling or avian species; namely, the depth axis is fundamentally different from the horizontal axis since hydrostatic pressure allows for direct sensing of position along the depth axis. Previous study has found that goldfish encode position using boundary vector cells, measuring distance and direction from salient features in the environment. A subset of these neurons, found in the central telencephalon of the goldfish brain, had firing rates that gradually increased or decreased with swimming depth, suggesting a gradual monotonic encoding of the fish's position in the depth dimension. Here, we investigated the contribution of hydrostatic pressure in these cells for position encoding in goldfish. We show results from two experimental assays- the first freely goldfish swimming in an invariant visual scene while varying the water level leading to changes in hydrostatic pressure. In the second experiment, we used an adjustable pressure chamber where other sensory cues remain constant. In both setups the neuronal activity of position encoding neurons was modulated by hydrostatic pressure variations. Using a hydrostatic cue for position encoding such as shown here provides a new perspective of place encoding in the brains of vertebrates, which might compensate for the need of fish to navigate in the underwater world.

**Disclosures: L. Cohen:** None. **E. Vinepinsky:** None. **O. Donchin:** None. **R. Segev:** None.

**Poster**

**PSTR054. Head Direction, View, and Spatially Modulated Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR054.09/UU28

**Topic:** H.09. Spatial Navigation

**Support:** DFG BU 3126/2-1
PR 2204/1-1
Athene (P.P.-F.)

**Title:** Sensory and behavioral modulation of the internal compass

**Authors: *E. BLANCO HERNANDEZ**, G. BALSAMO, P. PRESTON FERRER, A. BURGALOSSI;
Univ. of Tuebingen, Instituite of Neurobio., Tübingen, Germany

**Abstract:** Head-direction (HD) neurons are thought to contribute to hippocampal navigation and memory by providing a compass-like signal, which exclusively represents the animal's direction in space. We recorded from identified neurons in the anterior thalamus of awake mice and found that HD neurons reliably code for sensory stimuli with high temporal precision. Specifically, auditory and somatosensory stimuli evoked robust short-latency responses in identified HD cells, but not in non-HD neurons. The activity of HD cells, but not that of non-HD neurons, was also tightly correlated to spontaneous brain state fluctuations, showing precise coupling to pupil and whisker-pad motion dynamics. Social interactions dynamically modulated the gain of the HD representation, indicating that ethologically relevant behaviors engage these mechanisms. Collectively, our data show that sensory information and behavioral state map onto the HD representation, pointing to a new role for the internal compass in relaying sensory and behavioral features of experience into the hippocampal memory system.

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**Poster**

**PSTR054. Head Direction, View, and Spatially Modulated Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR054.10/VV1

**Topic:** H.09. Spatial Navigation

**Support:** CIHR Project Grant 155957
NSERC Discovery Grant RGPIN-2018-04600
Fonds de Recherche du Quebec, Sante

**Title:** Traveling activity in the head-direction cortex during sleep has an intrinsic neuronal origin

**Authors: *D. MEHROTRA**[1,2], D. LEVENSTEIN[2,3], A. J. DUSZKIEWICZ[4,5], S. A. BOOKER[5,6,7], A. KWIATKOWSKA[5,6,7], A. PEYRACHE[2];
[1]McGill Univ. Integrated Program in Neurosci., Montreal, QC, Canada; [2]Montreal Neurolog. Inst. and Hosp., Montreal, QC, Canada; [3]MILA, Montreal, QC, Canada; [4]Univ. of Stirling, Stirling, United Kingdom; [5]Ctr. for Discovery Brain Sci., [6]Simons Initiative for the Developing Brain, [7]Patrick Wild Ctr., Univ. of Edinburgh, Edinburgh, United Kingdom

**Abstract:** Sequential neuronal patterns and travelling wave-like activity are believed to support information processing in the cortex, yet their origin is still a matter of debate. We used 64-channel linear electrode arrays to conduct simultaneous population recordings along the DV axis of the head-direction cortex (HDC, i.e., post-subiculum) in adult male mice during sleep. As observed in other cortical areas, neuronal activity alternated between hyperpolarized DOWN states and activated UP states. Interestingly, HDC neurons were sequentially activated along the HDC dorso-ventral (DV) axis at the transition from DOWN to UP states. This travel originated locally at the UP-state onset as upstream thalamic nuclei shifted to UP states homogeneously. Decoded population activity also showed that the head-direction that was encoded during the sequential activation was preserved along the DV axis, suggesting that a common directional signal is conveyed downstream. To understand the mechanism underlying this gradient, we built a computational model with a linear array of recurrently connected units and compared the spatiotemporal properties of DOWN states generated by various biophysical gradients. The model uniquely matched experimental observations with a gradient in the strength of hyperpolarization-activated currents (Ih), which we confirmed in *ex vivo* slice experiments. Hence, varying amounts of Ih current across cortical neurons could result in travelling wave-like neuronal patterns, independent of other network properties. These findings open up the possibility that travelling activity upstream to the entorhinal-hippocampal formation organises large-scale neuronal activity supporting learning and memory during sleep.

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**Poster**

**PSTR054. Head Direction, View, and Spatially Modulated Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR054.11/VV2

**Topic:** H.09. Spatial Navigation

**Support:** CIHR Project Grant 155957
NSERC Discovery Grant RGPIN-2018-0460

**Title:** Neuronal activity in the medial entorhinal cortex is coordinated with thalamic head direction cells during wake and sleep

**Authors: *G. VITE**[1], Q. DING[1], B. HARTWICK[2], A. PEYRACHE[1];
[1]MNI, McGill Univ., Montreal, QC, Canada; [2]McGill Univ., Montreal, QC, Canada

**Abstract:** Successful navigation requires the production of signals that remain consistent, irrespective of changes in the environment. This can be achieved by constraining neuronal activity to low-dimensional subspaces that are mapped onto spatial features of an animal's behavior. During sleep, a period of reduced external input, pairwise coordination is maintained within different areas of the spatial navigation system. This coordination is notably seen between grid cells of the entorhinal cortex (MEC) and head-direction (HD) cells in the anterodorsal nucleus (ADn) of the thalamus. This supports the idea that activity in this network remains organized in all conditions. Since the ADn is necessary for the formation of grid cells, we hypothesized that the organization of neuronal activity within MEC requires a coherent HD input signal. To test this possibility, we performed simultaneous electrophysiological recordings in the ADn and MEC during periods of wakefulness and sleep. We first showed that coordination between HD cell pairs in ADn and MEC is preserved after environmental changes, as demonstrated in a cue rotation experiment. In addition, the preferred direction angular offset of ADn-MEC HD cell pairs predicted pairwise correlation during sleep. Lastly, the correlation among cell pairs in ADn was more stable over time, suggesting a more rigid structure in ADn compared to MEC. In conclusion, our findings suggest that organized activity in the MEC is, at least in part, controlled by the coherent HD signal arising from the ADn across brain states.
References: 1. Peyrache et al. (2015) Nat. Neurosci. 18, 569-575. 2. Gardner et al. (2019) Nat. Neurosci. 22, 598-608. 3. Winter et al. (2015) Science. 22, 870-874.

**Disclosures:** **G. Vite:** None. **Q. Ding:** None. **B. Hartwick:** None. **A. Peyrache:** None.

**Poster**

**PSTR054. Head Direction, View, and Spatially Modulated Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR054.12/VV3

**Topic:** H.09. Spatial Navigation

**Support:** Vanier CGS
CIHR Project Grant 155957
CIHR Project Grant 180330
NSERC Discovery Grant RGPIN-2018-04600

**Title:** Cortical head-direction cell activity is rigidly organized and stable across weeks

**Authors: *S. SKROMNE CARRASCO**[1], G. VIEJO[2], A. PEYRACHE[1];
[1]McGill Univ., Montreal, QC, Canada; [2]Simons foundation, Flatiron institute, New York, NY

**Abstract:** Primary sensory cortical areas are characterized by low-level representations of sensory inputs, but whether these representations are stable over a long period of time or whether they are continuously renewed is still unclear. The head-direction (HD) signal is essential for the

spatial navigation system, where it has previously been found that place representation is unstable over long periods of time. In the cortex, the HD signal is processed by the head-direction cortex (HDC – i.e. the postsubiculum). HD cells constitute a vast majority of HDC principal neurons. Each HD cell fires towards a specific direction of the head of the animal in the horizontal plane. To address the question of representational stability in this signal, we used one-photon calcium imaging with portable microscopes ('miniscopes') to longitudinally monitor ensembles of HD cells in the HDC over several months in freely moving mice both in single and multiple environments. We found the representation of the HD signal to be stable at two levels. First, the pairwise offset between HD neurons was preserved for months and across environments, indicating that the subcortical representation of the HD signal is certainly itself stable and that thalamocortical integration is rigid. Second, the orientation of the HD signal at the population level was maintained in a given environment over four consecutive weeks in a single environment. This orientation was preserved even when the environment was not explored for six weeks, suggesting that the HD system preserves long-term memories of spatial orientation in different environments. Last, we show that the stability of spatial orientation memories is retained even if environments are visited in a random weekly order. Similarly, stability remains even if an environment is visited only once a week or once a month. These findings shed light on how spatial information is represented over time in the brain's navigation system.

**Disclosures: S. Skromne Carrasco:** None. **G. Viejo:** None. **A. Peyrache:** None.

**Poster**

**PSTR054. Head Direction, View, and Spatially Modulated Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR054.13/VV4

**Topic:** H.09. Spatial Navigation

**Support:** CIHR Project Grant 155957
180330, NSERC Discovery Grant RGPIN-2018-04600

**Title:** Thalamic head-direction neurons are organized irrespective of their inputs

**Authors: *G. VIEJO**[1], S. SKROMNE CARRASCO[2], A. PEYRACHE[2];
[1]Flatiron institute, New York, NY; [2]McGill Univ., McGill Univ., Montreal, QC, Canada

**Abstract:** Continuous attractor networks support various cognitive functions, yet the neuronal dynamics and circuits supporting these dynamics in-vivo remain unclear. The HD circuit is a canonical example of such network. HD cells each fire for a specific direction of the animal's head. In the anterodorsal nucleus of the thalamus (ADn), HD cells project to the postsubiculum (PSB) located in the cortex and maintain their mutual coordination during sleep, when sensory inputs are virtually absent, supporting the view of an attractor-driven system.
The rigid organization of HD cell activity in the ADN begs the question of the origin of these structured patterns. The upstream structure, the lateral mammillary nucleus (LMN), is thought of

as a central component of the HD signal generator circuit and receives feedback from PSB. We thus investigated the organization of LMN activity across brain states, and its relationship to ADN and PSB. To this end, we recorded both ADN-LMN and PSB-LMN neuronal ensembles during exploration and sleep.
HD cells in the LMN during Rapid Eye Movement (REM) sleep were coordinated exactly as during exploration - as in the ADN and PSB. In contrast, during non-REM sleep, the coordination of LMN HD cells was reduced while simultaneously recorded ADN neurons or PSB neurons maintained the same level of mutual coherence. The decreased level of correlation in LMN resulted, at least in part, by a switch to hypersynchronous spiking activity in which neurons co-fired irrespective of their mutual preferred direction. Inter-spikes intervals (ISIs) during the transition to a preferred direction revealed a discrete activation of ADN neurons as opposed to a continuous activation of LMN neurons. More notably, the coordination of LMN activity was even lower when PSB was optogenetically inactivated during sleep, but not during wake, suggesting that LMN maintains a level of coordination that depends on PSB feedback in state-dependent manner. Our results suggest that non-linear integration of LMN inputs to ADN and cortical feedback from PSB are sufficient to maintain the coordinated activity in the ADN and the PSB during nREM sleep.

**Disclosures: G. Viejo:** None. **S. Skromne Carrasco:** None. **A. Peyrache:** None.

**Poster**

**PSTR054. Head Direction, View, and Spatially Modulated Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR054.14/VV5

**Topic:** H.09. Spatial Navigation

**Support:** CIHR Project Grant 155957
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FRQNT Strategic Clusters Program (2020- RS4-265502 - Centre UNIQUE - Union Neurosciences & Artificial Intelligence - Quebec
Richard and Edith Strauss Fellowship in Medicine

**Title:** A predictive learning model for cognitive maps that generate replay

**Authors: *D. LEVENSTEIN**[1,5], A. EFREMOV[1,5], R. H. EYONO[5,2], B. A. RICHARDS[3], A. PEYRACHE[4];

[2]Computer Sci., [3]Neurol. and Neurosurg., [4]Montreal Neurolog. Inst., [1]McGill Univ., Montreal, QC, Canada; [5]Mila, Montreal, QC, Canada

**Abstract:** The mammalian hippocampus contains a "cognitive map": a representation of an animal's environment that can be used to support navigation and generate offline simulations for the purposes of recall, planning, and the consolidation of memories. It has been hypothesized that this cognitive map relies on a network architecture in which excitatory connections between cells with similar spatial tuning produce an attractive neural manifold that reflects the structure of space, and that this spatial tuning can emerge from learning to predict sensory input. However, it remains unknown whether the spatial representation learned by predictive learning reflects an underlying attractor manifold that can produce replay, or whether predictive learning can produce a cognitive map in realistically complex environments wherein spatial location is non-trivially related to an animal's sensory data. We report that while spatially-tuned cells reliably emerge in recurrent neural networks trained to predict egocentric sensory input, the presence of spatially tuned cells is not sufficient to guarantee the presence of a cognitive map. Instead, the emergence of a cognitive map requires the use of recurrent connections to predict multi-step observation sequences in the presence of an orienting head direction signal. Once learned, this map can autonomously simulate plausible trajectories offline, which can be queried by the head direction signal and biased towards recently experienced locations to effectively "replay" those experiences. Motivated by these results, we develop a predictive RNN architecture inspired by the hippocampal theta oscillation, in which the cyclical prediction of sequences of future sensory input is used to rapidly form cognitive maps. Together, these results provide a unifying model for hippocampal functions and a platform for hippocampal-inspired approaches to artificial intelligence.

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**Poster**

**PSTR054. Head Direction, View, and Spatially Modulated Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR054.15/VV6

**Topic:** H.09. Spatial Navigation

**Support:** CIHR
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OGS
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**Title:** View cells in macaque hippocampus and lateral prefrontal cortex during virtual navigation

**Authors: *B. W. CORRIGAN**[1], R. GULLI[3], M. ROUSSY[2], M. ABBASS[2], G. DOUCET[4], B. MAHMOUDIAN[5], R. LUNA ALMEIDA[6], A. J. SACHS[7], J. C. MARTINEZ-TRUJILLO[8]; [1]Neurosci., [2]Univ. of Western Ontario, London, ON, Canada; [3]Columbia Univ., New York City, NY; [4]Ottawa Hlth. Res. Inst., Ottawa, ON, Canada; [5]Univ. of Western, London, ON, Canada; [6]Physiol., Univ. Autonoma de Chihuahua, Chihuahua, Mexico; [7]Neurosciences, Ottawa Hosp. Res. Inst., Ottawa, ON, Canada; [8]Schulich Sch. of Med. and Dentistry, Robarts Institute, Western Univ., London, ON, Canada

**Abstract:** View cells, cells that are selectively activated by a particular view of an environment, have been mainly described in the primate hippocampus (HPC), and area that integrates high level visual information from the dorsal and ventral pathways. Here we explore the possibility that view cells are also found in other brain areas than similarly integrate visual information from both pathways. We focus on the lateral prefrontal cortex (LPFC), which is located at the top of the visual processing hierarchy and assess view selectivity in both the HPC and the LPFC of macaques during a virtual environment task.

We trained four male macaques (*Macaca mulatta*) to use a joystick to navigate a virtual environment presented on a screen to complete a learning task where they had to chose between two discs and learn in which context which disc as better than the other. We tracked their eye position to verify where on the screen, and where in the virtual environment, they were looking. We recorded neural activity from the HPC in two animals, and the LPFC in the other two animals. We compared selectivity of single neurons for screen coordinates during two different task periods, where the animal held the same eye-on-screen position, but the view of the environment changed. We also used generalized linear models (GLM) to assess whether the colour of the object had any impact on the view selectivity. We used permutation tests to assess whether the coefficients were significant.

Neither area showed much selectivity for gaze directed at specific screen coordinates during navigation (where multiple parts of the environment were visible over the course of navigation), but HPC had 20% of cells that were selective for a view during the decision, and LPFC had 40% of cells selective. When we used a GLM to assess view and object colour at the same time, we found that 33% of HPC cells that were selective at all, were selective for object colour, but almost all of these had an interaction with view, with only 2% that were not affected by view. For the LPFC, 45% of the significant cells were selective for colour, but this time 8% had pure colour selectivity, and 35% had some selectivity for both view and colour, the majority having an interaction.

We described view selectivity of neurons from the HPC and LPFC of macaque monkeys in a virtual environment. Both areas have units that can be affected by changing small features of the view, like the task relevant object's colour, but most were unaffected by these changes and could be selective for the particular layout of the objects and the environment.

**Disclosures: B.W. Corrigan:** None. **R. Gulli:** None. **M. Roussy:** None. **M. Abbass:** None. **G. Doucet:** None. **B. Mahmoudian:** None. **R. Luna Almeida:** None. **A.J. Sachs:** None. **J.C. Martinez-Trujillo:** None.

**Poster**

**PSTR054. Head Direction, View, and Spatially Modulated Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR054.16/VV7

**Topic:** H.09. Spatial Navigation

**Support:** BrainsCAN
CIHR
NSERC

**Title:** Visual navigation strategies shape neuronal selectivities in the hippocampus of the common marmoset

**Authors: *D. B. PIZA**[1], B. CORRIGAN[2], R. GULLI[3], S. DO CARMO[4], A. CUELLO[5], L. MULLER[1], J. MARTINEZ-TRUJILLO[6];
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**Abstract: Introduction** Based on results of studies on spatial navigation in rodents, the hippocampus has been referred to as a Global Positioning System (GPS) where neurons selectivity for spatial locations (place cells) are essential components of a cognitive map of the environment (O'Keefe & Dostrovsky, 1971). However, studies conducted in other species such as primates have not fully to replicated the range of neuronal spatial selectivities found in the hippocampus of rats and mice during navigation tasks. Thus, it is unclear whether the analogy of the hippocampus as a GPS also applies to primates. In this study, we investigate the exploration strategies of marmosets during 3D navigation as we continuously tracked marmoset body position and head direction, and recorded wireless neural activity from the hippocampus (CA3 and CA1). We analyzed visual behavior correlates in single neuron, ensembles and local field potentials (LFP) and propose a mechanism that could support the formation of a visual cognitive map. **Results** We found that marmosets explore their environment via rapid head-gaze shifts while remaining stationary and then locomote toward targets minimizing such head-gaze movements. This is different from rats that mainly move the head at lower velocities as they locomote. We recorded a total of 331 neurons. A total of 204 cells were classified as putative pyramidal and 127 were classified as putative interneurons. We found a predominance of 3D view, head direction and place coding in putative pyramidal cells, and a mix of 3D angular head velocity (AHV) and translation speed (TS) in putative interneurons. We used a generalized additive model (GAM) to explore encoding of spatial and speed variables as either single or mixed encoding (encoding of multiple variables) by single neurons. Across all cell types, 48.3% significantly encoded at least one variable; amongst all encoding cells, mixed selectivity was predominant over single selectivity. In the putative pyramidal model, place was exclusively encoded in combination with either view or head direction. For the putative interneuron model, we found 73% mixed selective cells (AHV + TS). We report that rapid head movements 'reset' LFP theta oscillations in the hippocampus, which coincides with an increase in the response of interneurons followed by modulation of pyramidal neurons' firing. **Conclusion** Cognitive maps of space in the marmoset and likely in other primates may be driven by mixed coding of visual features used as landmarks for navigation. Head-gaze phase-resetting seems to play a role in

synchronizing theta oscillations to increase the efficiency of information encoding in the marmoset hippocampus.

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**Poster**

**PSTR054. Head Direction, View, and Spatially Modulated Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR054.17/VV8

**Topic:** H.09. Spatial Navigation

**Support:** R01MH132204

**Title:** Place representations and cognitive control in both dorsal hippocampus and cingulate cortex ensemble activity

**Authors: *G. J. BLAIR**[1], A. CHEUNG[2], E. PARK[1], A. A. FENTON[1];
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**Abstract:** Navigating our daily lives requires the judicious use of limited cognitive resources to yield preferred outcomes, called cognitive control, which is known in humans and animals to depend on the prefrontal cortex (PFC), including the anterior cingulate cortex (ACC). During a hippocampus-dependent (but not PFC) active place avoidance task to avoid a stationary shock zone on a slowly-rotating arena, ensemble recordings from dorsal hippocampus (HPC) show a robust cognitive control signal that alternates between representing the stationary or rotating locations every few seconds, matched to purposeful frame-specific spatial behavior. We performed single-photon miniscope calcium imaging in the ACC and HPC of freely-behaving rats to determine if a cognitive control signal is expressed in PFC ensemble discharge and whether it is coordinated with HPC discharge. Rats were transfected with AAV9-CaMKIIa-GCaMP8m in HPC dorsal CA1 and ACC, then gradient refractive index lenses were implanted above the injection sites. Rats were trained in the active place avoidance task on a rotating arena that can deliver a mild 0.2 mA shock in a 60° sector of the stationary room frame. Rotation requires rats to judiciously localize themselves and locations of shock within two reference frames at any time (the rotating *arena* frame comprised of local cues and the stationary *room* frame comprised of distal cues). Because room and arena cues continuously change their relationships, avoiding shock requires cognitive control. Rats readily learn frame-specific place avoidance and single-unit activity in both CA1 and ACC demonstrate strong location-specific activity. Analysis of the momentary positional information ($I_{pos}$) time series computed from separate CA1 and ACC ensembles express coherent spatial frame-specific representations of current location that flexibly alternate between the arena and room frames according to the rat's distance from the room shock zone, demonstrating cognitive control in both regions. Interestingly, this signal is present in ACC even though previous lesions of PFC do not impair

task acquisition or memory. This is the first demonstration of a *bona fide* cognitive control signal in rodent PFC, which during active place avoidance, like in HPC, changes along with spatial behavior after avoidance learning and appears more dispersed across ACC ensembles compared to CA1. The findings demonstrate both strong spatial and cognitive control representations in ACC and HPC, establishing a paradigm to investigate mechanisms of how two distinct brain circuits coordinate neural population activity during cognitive control of spatial information processing and memory.

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**Poster**

**PSTR054. Head Direction, View, and Spatially Modulated Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR054.18/VV9

**Topic:** H.09. Spatial Navigation

**Support:** PKMz and Engram cells, theory: R01MH132204, R01MH115304
Dynamics and Fmr1-null: R01NS105472

**Title:** Randomly connected excitation-inhibition coordinated networks account for diverse representational features of hippocampal ensembles

**Authors: *J. HURTADO**, C. SAVIN, A. A. FENTON;
New York Univ., Astoria, FL

**Abstract:** It is a general assumption that spatial representations in the Hippocampus (HPC) emerge from stereotyped connections and dedicated information channels, but the degree to which structured inputs are necessary for memory function in HPC is not known. We aim to investigate if unstructured connections are sufficient to reproduce features characteristic of the HPC, specifically, those we study in vivo such as mixed tuning, place cell remapping, memory-associated assemblies, and multiple place fields in large environments. We investigate the expressiveness of a simple leaky integrate and fire (LIF) recurrent neural network model of excitatory (E) neurons, with random multimodal positional tuning in the inputs along with random all-to-all fixed weights, and found that positional selectivity in the network can emerge from the random inputs by the introduction of LIF inhibitory (I) neurons. Parametrically increasing the homogeneous inhibitory weights abruptly switches the network from a disordered phase to an ordered phase, revealing sparse and spatially tuned excitatory assemblies firing in reliable sequences. During test simulations with stochastic behavioral trajectories, positions can be decoded from network activity using trial-averaged templates from training simulations with constant trajectories, and surprisingly, we also found temporal primacy representations organizing network activity based on rank ordered sequences of E activation (first to n spikes, n>5). These neuronal sequences can carry similar or sometimes greater average pairwise mutual information than the aforementioned spatial sequences. Moreover, cell-assemblies derived from

the top neurons in the temporal sequence can represent contextual information to downstream readers. Lastly, we show that the network can utilize a sparse, high firing rate assembly to represent special "reinforced" positions that are coupled to higher firing rates in the random inputs. Using this feature to naively probe for positional selectivity and train the network in a place memory task, we programmed learned associations between these high firing E assemblies and place avoidance (i.e. change direction) in one context, and associated a different context with freezing responses using relevant temporal primacy assemblies along with an aversive training signal, effectively training the network to recall correct responses (spatial avoidance and non-spatial freezing) in a context dependent manner after removing the training signals. Our findings suggest that the nonlinear dynamics of unstructured LIF networks with inhibition are expressive enough to model several features of memory in the HPC.

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**Poster**

**PSTR054. Head Direction, View, and Spatially Modulated Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR054.19/VV10

**Topic:** H.09. Spatial Navigation

**Support:** NIH R01NS105472
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**Title:** Transcriptional and PKMζ dysregulation in Fmr1 knockout mouse dentate gyrus one week after active place avoidance learning

**Authors: *J. HAN**[1,2], C. JOU[5,7], H. A. HOFMANN[2,3,4], A. A. FENTON[5,6];
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**Abstract:** Fragile X Syndrome is the most prevalent form of genetically caused intellectual disability and autism spectrum disorder due to a silencing mutation and consequent loss of fragile X messenger ribonucleoprotein 1 (FMRP). Loss of FMRP represses mRNA translation leading to activity-dependent abnormalities of synaptic function and plasticity, as well as cognitive inflexibility, but no clear impairments of learning and memory in the absence of cognitive conflict. FMRP loss also causes dysregulation of protein expression, indicating complex consequences of the mutation, likely involving compensatory changes. We thus investigated the transcriptomes of Fmr1-null mice that were killed 1-h after testing memory for an active place avoidance that was conditioned across 3 trials one week prior. The memory causes and requires persistent synaptic strengthening in hippocampal dentate gyrus (DG) and

Ammon's horn. We carried out RNA-seq analysis of the supra- and infra-pyramidal blades of DG in Fmr1-null (n=23 ea. sex) and wildtype (WT) mice (n=23 ea. sex); half the mice learned the place avoidance and half were yoked controls that had a physically similar experience as a trained mouse but experienced the shock in random locations. As expected, compared to WT, Fmr1 expression was significantly reduced in the null mice, yet learning-related behavior was similar between the genotypes. Using Weighted Gene Co-expression Network Analysis (WGCNA), we discovered that the activity of only one gene module (regulating cellular energy homeostasis) was dependent on genotype, possibly indicating compensatory processes in Fmr1-nulls. Similarly, only one module (involved in synapse organization) differed between trained and yoked mice. The activity of several modules involved in the glial function and synaptic transmission varied significantly between supraDG and infraDG. Finally, we analyzed the expression of candidate genes previously implicated in learning and memory processes, including Long-Term Potentiation (LTP), astrocyte function, and immediate-early genes. We note that Prkcz expression was significantly greater in supraDG than infraDG. Prkcz encodes the atypical protein kinase C isoform, PKMζ that is crucial for the persistence of WT LTP and the avoidance memory. Prkcz expression was also greater in Fmr1-nulls, and further increased after training, consistent with a crucial role for PKMζ in memory persistence. Taken together, our results demonstrate 1) transcriptional dysregulation in Fmr1-nulls, suggestive of compensation for loss of FMRP 2) transcriptional support for PKMζ's role in memory 3) the distinct value of both unbiased and candidate gene analyses.

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**Poster**

**PSTR054. Head Direction, View, and Spatially Modulated Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR054.20/VV11

**Topic:** H.09. Spatial Navigation

**Support:** R01NS105472
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Simons Collaboration for the Global Brain (SCGB)

**Title:** Subjective registration of the internal head-direction sense to the environment

**Authors: *S. CARRILLO SEGURA**[1], A. PAK[1], J. AARSE[2], D. ANGELAKI[1], A. FENTON[1]; [1]NYU Ctr. For Neural Sci., New York, NY; [2]Ruhr Univ. Bochum, Bochum, Germany

**Abstract:** Mammalian navigation relies on a cognitive map assumed to require a stable and accurate sense of allocentric direction that is anchored to physical environmental features for orienting ("north"). However, the sense of direction is subjective, internally-organized, and persistent in the absence of external stimuli, which can make navigation inaccurate. In this work, we recorded large ensembles of cells (n~150) from the anterior dorsal nucleus of the thalamus in

freely-behaving and head-fixed mice. In the absence of vestibular stimulation, the head-fixed mice navigated a cue-rich environment on an air cushion. Using the IsoMap algorithm, we projected the ensemble spike trains into a 2-dimensional neural ensemble-activity space, which revealed a head-direction (HD)-ring manifold population geometry. The head-fixed HD-ring collapsed during stillness, but was normal during active locomotion, even though single cell HD tuning was lost, compared to freely-behaving. The head-fixed HD-ring dynamics persisted but did not stably anchor to external environmental features, as evidenced by unchanged cell cofiring on sub-second time scales because of subjective, transient, multistable registrations of the internal direction sense to different allocentric bearings. A continuous attractor model confirmed that the observations can be explained by a dynamically erroneous estimation of angular head velocity during head-fixation. Because the internally-organized head direction sense is not stably anchored to an allocentric bearing, it can shift episodically and subjectively to create what would appear to an external observer as inaccurate navigation. These findings challenge the standard model of the stable, reliable, allocentrically anchored head direction sense, and emphasize its subjectivity, internal organization, and independence from external stimuli.

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**Poster**

**PSTR054. Head Direction, View, and Spatially Modulated Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR054.21/VV12

**Topic:** H.09. Spatial Navigation

**Support:** R01NS105472
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**Title:** Neurodiversity and cognitive competence in the Fmr1-null mouse model of Fragile X Syndrome

**Authors: *A. A. FENTON**[1], D. DVORAK[1,2], A. CHUNG[1,3];
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**Abstract:** Mutations that silence the Fragile X Messenger Ribonucleoprotein 1 (FMR1) gene cause Fragile X Syndrome, the most common genetic cause of autism and intellectual disability. *Fmr1*-null mutant rodents do not express the protein FMRP, modeling the genetic defect. *Fmr1*-nulls express numerous neurobiological abnormalities, and behavioral deficits, compared to wild-type. We reported abnormal experience-induced synaptic function and plasticity changes but normal hippocampus CA1 place cell firing fields and abnormally coordinated discharge amongst principal cells and interneurons in *Fmr1*-null CA1 compared to wild-type. Because complex systems afford multiple solutions to most problems, we considered the hypothesis that

instead of being deficits, neurobiological abnormalities in *Fmr1*-nulls indicate diverse ways that the *Fmr1*-null brain can accomplish cognitive behavioral goals. We examined *Fmr1*-null mice in object and social recognition memory tasks, and recorded source-localized hippocampal local field potentials during active an place avoidance task that requires cognitive control of spatial information and memory, and is one of the most sensitive tasks to hippocampal dysfunction. Because medial perforant path (MPP)-originating dentate spikes (DSm) initiate hippocampus-wide coordinated neural activity and information recollection, we examined DSm and lateral perforant path (LPP)-originating dentate spike (DSl) prevalence during home-cage and active place avoidance behaviors, in addition to how the avoidance training changes MPP synaptic responses. *Fmr1*-null mice are competent at each task, despite differing from wild-type. Both *in vivo* DSm and MPP-synaptic responses in dentate gyrus are also different from wild-type; in the supra- but not the infra-pyramidal blade of dentate gyrus, avoidance training weakens wild-type MPP fEPSPs to the level of fEPSPs of task-naïve *Fmr1*-nulls, which do not change with training. The ratio of DSm/DSl is elevated in *Fmr1*-nulls in the home cage and during place avoidance. *Fmr1*-null rates of sharp wave ripples are like wild-type during place avoidance training, but excessive in the home cage after a 24-h retention test. Thus *Fmr1*-null mice express neurodiverse systems-level neurophysiology and social behavior differences, but also equally competent cognitive abilities compared to wild-type. The findings challenge our presuppositions that the differences are deficits, and indicate that *Fmr1*-null mice may be better understood as neurodiverse and cognitively competent, rather than impaired.

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**Poster**

**PSTR054. Head Direction, View, and Spatially Modulated Cells**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR054.22/VV13

**Topic:** H.09. Spatial Navigation

**Title:** Improved coding of head direction and spatial location during spatial learning in the morris water maze are differentially affected by loss of long-term potentiation

**Authors: *R. RESHEF**[1,2], M. SHAHI[1,3], T. J. O'DELL[1,4], D. AHARONI[1,2], P. GOLSHANI[1,2]; [2]Dept. of Neurol., [3]Dept. of Bioengineering, [4]Dept. of Physiol., [1]UCLA, Los Angeles, CA

**Abstract:** Learning and memory enables the organism to update knowledge of the world through experience and allows it to navigate through a myriad of stimuli to facilitate survival. Lesions or inactivation of the hippocampus impair the encoding and retrieval of spatial memories. Hippocampal place and head direction (HD) cells activity have long been proposed to represent one’s location and heading direction in space. Yet, how place and HD neuronal population dynamics change with spatial learning and how this activity drives navigation to a learned goal is poorly understood. To address these questions, using wire-free miniaturized microscopy of GCAMP7f**,** we imaged the activity of CA1 neurons during spatial learning of a target oriented

two-dimensional navigational task, the Morris Water Maze - a gold standard task for spatial navigation. Using generalized linear models (GLM) we were able to disentangle the activity of place cells and HD cells in CA1 as animals navigate in the maze. Our results demonstrate that the tuning of space and HD cells becomes significantly more selective as mice learn to navigate to the goal (n=5 animals). Concomitantly, the prediction of spatial location and HD from the population activity using deep learning-based decoding methods showed a significant improvement after learning. To investigate the plasticity mechanisms driving our results, we performed identical experiments in GluA1$^{C2KI}$ knock-in mice and their controls, these mice have been shown to have impaired Schaffer collateral long-term potentiation (LTP) in CA1 without any deficiency in the basal synaptic transmission (Zhou et al., 2018). We first confirmed loss of 100 Hz tetanus-induced LTP in knock-in mice. Our preliminary results show that in contrast to WT littermate controls, HD selectivity did not increase in LTP-deficient mice (n=3 mice) during learning. Conversely, spatial selectivity improved during learning to a similar extent to what was measured in controls. Consistently, decoding of HD from population activity did not improve with learning in LTP-deficient mice while it improved in controls. In contrast, decoding of spatial location improved to a similar extent in LTP-deficient mice and controls. Surprisingly, our preliminary results show faster navigational learning in LTP-deficient mice (as measured by escape latencies) as compared to their controls and similar target quadrant occupancy in probe trials. Therefore, while LTP is necessary for the improvement of HD, this improvement was not essential for spatial navigation learning. Further experiments will explore the improvement in spatial tuning of CA1 neurons during learning, and whether it is critical for learning.

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**Poster**

**PSTR055. Behavior and Symptoms of Psychosis**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR055.01/VV14

**Topic:** H.13. Schizophrenia

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Japan Society for the Promotion of Science KAKENHI No. 20K03490, 23K03024, 20H03610

**Title:** Impaired active inference in schizophrenia is linked to reduced sensitivity of pupillary response to prediction uncertainty

**Authors:** *T. SUMIYOSHI, **A. SHIRAMA**;
Dept. of Preventive Intervention for Psychiatric Disorders, Natl. Ctr. of Neurol. and Psychiatry, Tokyo, Japan

**Abstract:** Humans adaptively infer the nature of the surrounding environment based on observational sensory data. The arousal system is thought to play an important role in the encoding of uncertainty which is essential in determining the confidence in predicting what will or will not happen next. Recent computational models assume psychotic symptoms, such as delusions and hallucinations, are a cause of maladaptive inferences. However, little is known about the neural mechanisms underlying the disturbance of inference processes in patients with schizophrenia. To address this issue, we compared the performance on an active inference task between schizophrenia patients (N=25) and healthy controls (N=25), and concurrently measured pupil diameters, a parameter thought to predict uncertainty when performing an active inference task. In the active inference task, participants were instructed to predict each subsequent number to be presented in a series, such that the average error made on all predictions would be minimized. Participants were required to rely directly on unobservable task representations to estimate the likely outcomes, and update their predictions at several discrete change points in which an outcome generation criterion was changed. We found that healthy controls tended to provide values which were closer to the mean on the outcome-generating distribution right after a change point. However, schizophrenia patients showed difficulty in the convergence of prediction indicating an inaccurate estimation of the outcome-generating distribution. Furthermore, the trial-wise pupil dilation changed its association with trial-wise uncertainty, as estimated by an optimal Bayesian inference model, in a performance dependent fashion in the healthy control group, but not in the schizophrenia group. These findings suggest that impaired active inference in patients with schizophrenia is linked to altered noradrenergic responsivity to prediction uncertainty.

**Disclosures:** **T. Sumiyoshi:** None. **A. Shirama:** None.

**Poster**

**PSTR055. Behavior and Symptoms of Psychosis**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR055.02/VV15

**Topic:** H.13. Schizophrenia

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**Title:** Continuous inhibition of N-methyl-D-aspartate (NMDA) receptors with ketamine predominantly affects male rather than female mice.

**Authors: *A. O. CUELLAR SANTOYO**[1], O. RANGEL PEREZ[2], A. E. MIRELES NAVARRO[1], V. M. RUIZ RODRÍGUEZ[1], A. G. HOWE[3], E. O. PORTILLO JERONIMO[1], L. Y. ISLAS CASTILLO[1], M. R. FLORES GONZÁLEZ[1], T. B. MARES BARBOSA[1,4], A. PATRON SOBERANO[1], A. M. ESTRADA SÁNCHEZ[1];
[1]Biología Mol., Inst. Potosino de Investigación Científica y Tecnológica, San Luis Potosi, Mexico; [2]Ctr. Nacional de Supercomputo, Inst. Potosino de Investigación Científica y Tecnológica, San Luis Potosí, Mexico; [3]Intelligent Systems Lab., Malibú, CA; [4]Translational and Mol. Med. Lab., Univ. Autonoma de San Luis Potosí, San Luis Potosí, Mexico

**Abstract:** Ketamine is a non-competitive inhibitor of the glutamatergic N-methyl-D-aspartate (NMDA) receptors. It is commonly used as an anesthetic, a treatment for depression, as a recreational drug and even as a pharmacological model of schizophrenia. However, it is currently unclear whether extended exposure to ketamine impacts behavior and whether this impact differs based on gender. Therefore, we evaluated the outcome of continuous administration of ketamine (14 consecutive days at 30 mg/kg) on the performance of C57BL/6J male and female mice in different behavioral tests. These tests evaluated memory, social interaction, anxiety, movement, and executive function. We analyzed each behavioral test with DeepLabCut, a program that utilizes a Deep-neural-network to track the movement of the mice and provides precise information on mouse position. According to the results, continuous administration of ketamine impaired the performance of male and female mice in the novel object recognition test, which assesses short-term memory. Interestingly, this effect was more pronounced in males. Ketamine also affected social interaction since we observed decreased frequency and reduced duration of mice interaction intervals. Like the novel object recognition test, the effect of ketamine on social interaction was more pronounced in male mice compared with females. On the contrary, no significant effect of ketamine or gender was detected in the light/dark transition test (anxiety); the wheel maze test (motor system); and the puzzle box test (executive function). Altogether, these results suggest that continuous ketamine administration affects brain regions related to memory and social interaction, such as hippocampus, amygdala, and cortex, and that ketamine effects are more pronounced in male than female mice.

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**Poster**

**PSTR055. Behavior and Symptoms of Psychosis**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

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**Topic:** H.13. Schizophrenia

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**Title:** Mechanism of delusion and hallucination in schizophrenia based on the quadripartite model

**Authors: *M. KUO**, A.-C. YANG;
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**Abstract: Background:** Delusion and hallucination are common symptoms in schizophrenia(SCZ).Several researches also demonstrated collaborative neural underpinningregarding delusion and hallucination. The intrinsic networks based on the triplenetwork theory (i.e.,default mode, salience, central executive network)are recruitedduring delusional or hallucinatory phenomena, reflecting some brain modules mightbe overlapped when the symptoms arise. A quadripartite model trying to explain theprocess during hallucinations, might also be interpretable for delusions due to itsinvolvement of the aforementioned triple network and hippocampus. Moreover, theprecise prediction of these two symptoms is not yet understood. We hypothesized thecrucial differences between delusion and hallucination might be detected throughaforementioned brain networks and provide as key features for machine-learningmodels to classify SCZ and healthy controls.**Methods:** A total of 341 HC and 213 SCZ patients were recruited in this study.Ensemble empirical mode decomposition was employed to decompose voxel-wisedresting-state functional Magnetic Resonance Imaging (rs-fMRI)data into intrinsicmode functions (IMFs)within regions according to the quadripartite model. Wetrained multiple classifiers with the various features extracting from the IMFs,including instantaneous frequency, amplitude, and phase, as well as mean frequency,amplitude, standard deviation and sample entropy of rs-fMRI data.**Results:** In hippocampus, the detection of SCZ could be well predicted via originalvoxel-based rs-fMRI signal of instantaneous amplitude and frequency with theF1-socre of 1 by multiple models (e.g.,KNN, logistic and SVM models).Furthermore, linear discriminant analysis model performed best in IMF4 ofinstantaneous frequency with the F1-score of 0.86 for detection of delusion; whilelogistic model performed ideally in IMF2 of sample entropy with the F1-score of 0.95for detection of hallucination. Naive Bayse model with IMF2 of instantaneousfrequency had the F1-score of 0.87 for predicting both symptoms.**Conclusion:** Our study shows the precise diagnosis for SCZ is feasible. In addition,the prediction of delusion and hallucination help to clarify the influence from onebrain network to another, which might indirectly shed light on the network dynamicsand structural connectivity.

**Disclosures: M. Kuo:** None. **A. Yang:** None.

**Poster**

**PSTR055. Behavior and Symptoms of Psychosis**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR055.04/VV17

**Topic:** H.13. Schizophrenia

**Support:** Czech Health Research Council (AZV CR): NU21-04-00405
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Charles University Grant Agency (GA UK) 1313820
Charles University Grant Agency (GA UK) 1070119

**Title:** Gnathonemus petersii fish display positive and cognitive schizophrenia-like symptoms in reaction to ketamine

**Authors: *V. LANGOVA**[1,2], P. HORKA[3], J. HUBENY[1], T. NOVAK[1], K. VALES[1], P. ADAMEK[1,2], K. HOLUBOVA[3], J. HORACEK[1,2];
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**Abstract:** The idea of the *Gnathonemus petersii* (*G. petersii*) species elevating the modelling of schizophrenia is based on the fish's electrolocation and electrocommunication abilities enriching the modelling of all, positive, cognitive and negative schizophrenia symptoms including specific symptoms, which are untreatable using current medication. We exposed 24 individuals of *G. petersii* species to the NMDA antagonist ketamine in two distinct series differing in the dose of ketamine. The main finding revealed ketamine-induced disruption of the relationship between electric signalling and behaviour indicating impairment of fish navigation as an animal analogue to cognitive symptoms of schizophrenia. Moreover, the lower dose of ketamine significantly increased locomotion and erratic movement, whereas the higher dose of ketamine significantly reduced the number of electric organ discharges, both indicating successful induction of positive schizophrenia-like symptoms. Additionally, a low dose of haloperidol was used to test the normalisation of the positive symptoms to suggest a predictive validity of the model. However, though successfully induced, positive symptoms were not normalised using the low dose of haloperidol; hence, more doses of the typical antipsychotic haloperidol and probably also of a representative of atypical antipsychotic drugs need to be examined in the future to confirm the predictive validity of the model.

**Disclosures:** **V. Langova:** A. Employment/Salary (full or part-time); National Institute of Mental Health, Topolova 748, 250 67 Klecany, Czech Republic, Third Faculty of Medicine, Charles University, Ruska 87, 100 00 Prague, Czech Republic. 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.; Charles University Grant Agency (GA UK): 1313820. **P. Horka:** A. Employment/Salary (full or part-time); Institute for Environmental Studies, Faculty of Science, Charles University, Albertov 6, 128 00 Prague, Czech Republic. 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.; Czech Health Research Council (AZV CR): NU21-04-00405. **J. Hubeny:** A. Employment/Salary (full or part-time); National Institute of Mental Health, Topolova 748, 250 67 Klecany, Czech Republic. B. Contracted Research/Research Grant

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**Poster**

**PSTR055. Behavior and Symptoms of Psychosis**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR055.05/VV18

**Topic:** H.13. Schizophrenia

**Support:** NIH Grant 5R01MH120089-04

**Title:** Computational comparison of aberrant learning accompanying paranoid and delusional beliefs

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**Abstract:** Early identification of individuals who at clinical high risk (CHR) for developing psychosis can improve prognosis, however, that identification is imprecise and subjective. We address those issues by administering quantitative behavioral tasks to a sample that includes CHR individuals (N = 154) as well as matched psychiatric controls (N = 139), and healthy controls (N = 100) along with assessments to measure paranoia, delusions, and other psychiatric symptoms. Task performance is paired with generative computational modeling, which warrants inferences about participants' beliefs and belief-updating. We compare learning on two different cognitive tasks, probabilistic reversal learning (PRL) and Kamin blocking, that have shown relationships to paranoia and delusions, respectively. We find that CHR status does not result in different behavior on the PRL ($p = 0.81$), but that an individual's level of paranoia is associated with excessive switching behavior ($p < 0.001$). During the blocking task, paranoid individuals did not significantly learn differently about the blocked cue ($p = 0.09$). However, they also had decreased learning about the control cue, suggesting more general learning impairments ($p = 0.015$). Delusions were associated with aberrant learning about the blocked cue ($p = 0.015$) but intact learning about the control cue ($p = 0.47$), suggesting specific impairments in learning related to cue combination. We fit task-specific computational models to behavioral data to explore how latent parameters vary within individuals between tasks, and how they can explain symptom-specific effects. We use a Hierarchical Gaussian Filter (HGF) model for PRL data, allowing for tracking volatility-driven belief-updating. For the blocking task, we utilize a modified Rescorla-Wagner model with a Pierce-Hall learning rate that updates stimuli representations throughout the task. We find that paranoia is associated with a decreased value of a parameter controlling volatility belief-updating (more rigid volatility beliefs) in the PRL ($p = 0.0022$), as well as low dynamic learning rates in the blocking task ($p = 0.023$). For the blocking task, delusions were related to a parameter, , which controls the degree and direction of similarity between cue updating during simultaneous cue presentation. Delusions were associated with increased update similarity for the separate elements of compound cues ($r = -0.12$, $p = 0.021$). These results suggest that paranoia and delusions involve dissociable deficits in learning and belief updating, which - given the transdiagnostic status of paranoia - may have differential utility in predicting psychosis.

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**Poster**

**PSTR055. Behavior and Symptoms of Psychosis**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR055.06/VV19

**Topic:** H.13. Schizophrenia

**Support:** Psi Chi Undergraduate 2023 Research Grant
John ’94 and Ann McAllister Albright Creative Research Experience Scholarship

**Title:** Impact of Virtual Reality (VR) Simulations and Written Prompts on Stress Responses and Attitudes toward Schizophrenia

**Authors: *S. ZOLYNSKI**, K. FEIGENSON;
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**Abstract:** Stigma and misunderstanding often surround schizophrenia (SCZ), leading to challenges in patient care and social integration. We aimed to address this problem by investigating the efficacy of virtual reality (VR) simulations and written prompts in fostering empathy and attitudes towards SCZ, with an emphasis on how stress levels (measured with salivary cortisol) could influence in empathy change. There were 7 male, 34 female, and 3 non-binary participants, randomly assigned to 1 of 4 conditions for a 2 (VR with and without sound) x 2 (SCZ prompt and no SCZ prompt) mixed ANOVA design. The VR conditions were 2 episodes of individuals experiencing SCZ episodes from a 1$^{st}$ person perspective, including auditory hallucinations. The control condition contained the same videos without sound. Empathy levels were measured with the Attitudes Toward SCZ Questionnaire (ATSQ) and the Multidimensional Emotional Empathy Scale (MDEES). Stress was assessed via cortisol pre and post-intervention by ELISA. Written prompts depicted challenges for an individual with SCZ vs. a control individual experiencing daily stressors.A borderline significant difference in in the ATSQ was observed in the SCZ ($M$ = 67.60, $SD$ = 8.35) compared to the control prompt condition ($M$ = 62.05, $SD$ = 11.29), [$F$(1,36) =3.920, $p$ = .055]. Cortisol remained stable across time points and conditions ($p$s > .05). MDEES scores were consistent across all conditions ($p$s > .05). However, when we included proximity to someone with SCZ as a variable, that created significant differences for the MDEES and the ATSQ independent of manipulation ($t$s > 2.16, $p$s < .037), where both were higher in participants who knew someone with SCZ.The findings suggest that, contrary to expectations, VR did not significantly alter cortisol levels. Written prompts, however, demonstrated the potential to increase ATSQ scores. The findings with personal relationships underline the value of real-life experiences in shaping attitudes. These observations have considerable implications for VR based training approaches. Specifically, while VR can provide a safe and controlled environment for healthcare professionals, they likely cannot replace lived experiences connecting with real people. A significant limitation in the present study was the user could not interact with the environment of the simulation. However, advancements in virtual and augmented reality may provide more visceral methods for experiencing diverse individual perspectives. Therefore, while these strategies can and should be adapted in tandem with developing technologies, integrating real person interaction could significantly boost empathy development.

**Disclosures:** **S. Zolynski:** None. **K. Feigenson:** A. Employment/Salary (full or part-time); Albright College.

**Poster**

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**Program #/Poster #:** PSTR055.07/VV20

**Topic:** H.13. Schizophrenia

**Support:** P50 MH119569
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**Title:** Clarifying proactive and reactive cognitive control deficits in psychosis via drift diffusion modeling

**Authors: *O. CALVIN**[1], C. SHEN[2], E. RAWLS[3], A. D. REDISH[1], S. R. SPONHEIM[4,3]; [1]Neurosci., [2]Dept. of Psychology, [3]Dept. of Psychiatry and Behavioral Sci., Univ. of Minnesota, Minneapolis, MN; [4]Mental Hlth., Minneapolis VA Healthcare Syst., Minneapolis, MN

**Abstract:** Individuals with schizophrenia and other psychosis disorders have consistent deficits in cognitive control. People with psychosis typically exhibit lower accuracy rates when using proactive and reactive control, but researchers have also noted slower reaction times. To better understand the underlying mechanism that produces these proactive and reactive cognitive control deficits in psychosis we decided to take an evidence integration perspective. We fit hierarchical drift diffusion models to the behavior of participants from the Psychosis Human Connectome Project (123 with psychosis, 70 first-degree relatives, and 51 controls) on a cognitive control task, and then used XGBoost classification to determine which of these parameters were most informative for differentiating between groups.
Participants performed the dot pattern expectancy (DPX) task, in which participants are provided sequences of cue-probe pairs that require different responses to the probe given a cue. Cues (A or B) were followed by probes (X or Y) after a delay of 2.5-3.5 s. The predominant AX sequence (60% of trials) required one response, while the AY, BX, and BY sequences required another. Drift diffusion models separate the evidence integration process into four independent components: drift rate - v, response threshold - a, non-decision time - t, and response bias - w. In the hierarchical model, we permitted the drift rate, response threshold, and non-decision time to vary by sequence type and the response bias to vary by the cue.
We found that people with psychosis showed slower drift rates when utilizing proactive control (BX, BY conditions) and longer non-decision times than controls and relatives on oddball trials (AY, BX, BY conditions). The XGBoost classification model found that the most important parameters for differentiating between the groups were, in order of utility, the degree of bias on proactive control trials (w-B), the drift rate on proactive control trials (v-BY), and the non-decision time on incongruent trials (t-AY, t-BX). The XGBoost classification of DDM parameters better differentiated group membership than traditional measures (i.e., accuracy, mean reaction times, d'-context and the proactive behavioral index). We found that d′-context, an ubiquitously used measure of contextual processing, was less useful for differentiating between

individuals with and without psychosis than raw reaction times and error rates. These analyses suggest that cognitive control deficits in individuals with psychosis are best characterized as slower evidence integration and longer motor-preparation/perceptual times.

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**Poster**

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**Topic:** H.13. Schizophrenia

**Support:** CIHR
NSERC

**Title:** Exploring the Interaction of Early Life Stress and Maternal Cannabis Exposure During Pregnancy: Evidence for the Double-Hit Hypothesis of Schizophrenia

**Authors: *E. PÉREZ-VALENZUELA**, D. HARDY, S. R. LAVIOLETTE, W. J. RUSHLOW; Univ. of Western Ontario, London, ON, Canada

**Abstract:** Cannabis is the most commonly used illicit drug worldwide, with a past-month prevalence of 5%. Between 2009-2016, cannabis use prevalence during pregnancy has risen 19% in young women (18-24 years), with smoking and edibles being the most popular routes of administration. Furthermore, mothers who use cannabis are more distant, rejecting and withdrawn from their children than non-using mothers. Clinical studies have shown a dose-response relationship between childhood trauma and psychotic symptoms. In addition, prenatal cannabis might increase susceptibility to co-occurring environmental stressors during or after prenatal life, amplifying the risk of schizophrenia in later life. This combination represents a "double-hit" hypothesis for schizophrenia risk in children, whereby a prenatal neurodevelopmental insult might make offspring more vulnerable to environmental stressors postnatally, dramatically increasing disease risk. This research aims to assess the long-term consequences of prenatal THC exposure and early stress exposure in the context of schizophrenia risk and to determine the neuronal and molecular mechanisms associated with these exposures. We hypothesized that prenatal THC edible exposure might potentiate the long-term impairments induced by early life stress in offspring and increase risk factors associated with schizophrenia. Specifically, we propose that prenatal Δ9-THC exposure will dysregulate neuronal activity states and activate multiple molecular signalling pathways associated with schizophrenia risk in the PFC-HIPP circuitry. Pregnant Wistar rats were exposed to edible THC (5 mg/kg) or vehicle during the gestational day (GD) 7 to 2. Then, the litters were separated into two groups; a maternal separation group (daily 3 hours of maternal separation, from postnatal day 2 to 15) and a control. Then, male and female offspring's behavioural phenotypes were

examined during adolescence and adulthood using the following pre-clinical tasks: sucrose preference, social interaction, novel object recognition, open field, and pre-pulse inhibition. After behavioural testing, rats were assigned for western blot or electrophysiological analyses. Tissue extractions were taken from the prefrontal cortex (PFC) and ventral hippocampus. Then, the expression levels of several schizophrenia-related risk markers, including the AKT/GSK3 pathway, dopamine receptor expression and markers of GABA and glutamatergic signalling, were analyzed. PFC and ventral hippocampus neurons were recorded for electrophysiological studies, and single-unit activity patterns were analyzed.

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**Poster**

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**Title:** The connection between parasympathetic regulation and cognition in patients with schizophrenia and bipolar disorder

**Authors: *M. LAZARIDI**[1,2], E. KALISPERAKIS[2], V. GARYFALLI[2], T. KARANTINOS[2], A. MANTAS[2], P. FILNTISIS[4], N. EFTHYMIOU[4], A. ZLANTITSI[4], C. GAROUFIS[4], P. MARAGOS[4], N. SMYRNIS[5,3];
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**Abstract:** The association between cardiovascular activity levels and cognitive performance was examined in 36 adults with psychotic disorders with average age 30,2 years (SD=7,18). As part of the “e-Prevention” project, 18 male and 5 female adults with schizophrenia, as well as 6 male and 7 female adults with bipolar disorder carried a commercial smartwatch (Samsung Gear S3) with multiple sensors of biometric data for a long period of 24 consecutive months. Cardiovascular activity was continuously measured with photoplethysmogram. After data collection, long-and short-term diurnal changes of heart rate variability (hrv) were calculated as indexes of autonomic activity. Upon the beginning of the study, an extensive neuropsychological

battery was administered covering domains of cognition (speed of processing, working memory, sustained attention, set shifting, cognitive inhibition, verbal learning, verbal fluency, vocabulary). Based on Neurovisceral Integration model, which suggests a neural connection between cortical brain areas that are involved in executive functions, subcortical areas that are involved in autonomic regulation and the heart via the vagus nerve, we attempted to explore the connection between the high frequency component of heart rate variability (hf-hrv), which is indicative of parasympathetic regulation and cognitive performance. Our results show a significant correlation between hf-hrv measured during sleep, but not waking hours performance in Verbal Fluency test only for patients with schizophrenia (Controlled Oral Word Association Test COWAT) ($r = 0.57$, $p < 0.05$). Besides, preliminary analysis of the performance on an inhibitory task (Go/ No Go) shows a specific relation between parasympathetic regulation and cognitive stability (intra-individual variation of response latency) again only in schizophrenia patients ($r = -0.53$, $p < 0.05$). These results suggest a common underlying neurophysiological mechanism connecting physiological regulation and cognitive ability.

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**Poster**

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**Topic:** H.13. Schizophrenia

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**Title:** Priors & Delusions in Clinical High-Risk for Psychosis

**Authors: *S. BAKER**[1], S. MESSER[2], R. R. GIRGIS[3], G. HORGA[4];
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**Abstract: Priors and Delusions in Clinical High-Risk for Psychosis Authors *Seth Baker[1,2,3]**, Sylvie J. Messer[1,2,4], Ragy R. Girgis[1,2], G. Horga[1,2]; [1]New York State Psychiatric Institute, New York, NY; [2]Psychiatry, Columbia Univ., New York, NY; [3]Jacobs School of Medicine, Univ. at Buffalo, Buffalo, NY; [4]Ferkauf Graduate School of Psychology, Yeshiva Univ., Bronx, NY **Disclosures (all authors) None**
Delusions are defined as false beliefs maintained with conviction in the face of contradictory evidence and are one of the core symptoms of psychosis. We have shown that alterations in inference may underlie delusional pathology in schizophrenia, and have proposed an inferential

failure mode which offers a parsimonious model for delusion formation and maintenance. In this study, we aim to investigate whether delusions in those at clinical high-risk (CHR) for psychosis can be explained by similar inference alterations. We carried out an established, incentivized information sampling task (a modified beads task) in a sample of CHR individuals (n=43). In this task, participants chose whether to guess the identity of a hidden jar (one of two possible choices) or to sample information from it which might inform their guess, while reporting probability estimates for the hidden jar's identity at each stage of the task. Different experimental conditions featured jars with different bead ratios (e.g. 60:40 vs 90:10). As in our previous study in schizophrenia, we found an association between delusional ideation and increased information sampling (i.e. increased draws-to-decision slope across conditions; Pearson r=0.26, p=0.048). Model-based analyses of probability estimates drew from a formal model comparison which produced a winning Bayesian model variant with a single prior weight parameter , capturing primacy and recency biases over prior beliefs, as well as different likelihood weight parameters for each experimental condition. Of these parameters only the prior weight correlated with delusional ideation (Pearson r=0.27, p=0.038), just as in our previous work. Further analysis of choice behavior using a partially-observed Markov decision process (POMDP) model revealed that, among all model parameters, only this prior weight correlated with both delusional ideation and information-seeking (Pearson r=0.28, p=0.034). Our results suggest that a common mechanism underlies the delusional pathology experienced by CHR individuals and those experiencing full-blown psychosis, and are consistent with the notion that an inferential mechanism characterized by prior overweighting underlies the development of delusions as well as their maintenance.

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**Poster**

**PSTR055. Behavior and Symptoms of Psychosis**

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**Topic:** H.13. Schizophrenia

**Support:** R01MH117323
R01MH114965

**Title:** Alterations in perceptual processing and midbrain dopaminergic changes drive speech hallucinations in patients with schizophrenia

**Authors: *J. BUCK**[1,2], I. AITSAHALIA[1,2], D. SERRANO[3], G. HORGA[2,1];
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**Abstract:** Hallucinations are common in clinical and nonclinical groups, can be difficult to treat, and often predict poor functioning. Excess striatal dopamine has been strongly implicated in the

development of hallucinations but the precise circuits and cognitive processes that link this neurochemical alteration to false perception remain unclear. Here, medication-free patients with schizophrenia (N=68) in the fMRI scanner were presented with speech, non-speech, and blank stimuli at varying probabilities in a blocked structure and were asked to report when they heard speech. Speech false alarms during the task specifically correlated with hallucination severity but not negative symptoms or general psychopathology (partial Spearman $\boldsymbol{\rho}$;=0.37; p=2.44x10$^{-3}$). Speech false alarm rates also significantly varied with the block probability manipulation (mixed effects logistic regression p=1.14x10$^{-5}$). To clarify this finding, we built a computational learning model that updates trial-by-trial speech expectations and integrates these expectations with current sensory evidence and a perceptual bias term to form a percept. Fitting the model to response data showed that individual biases correlated with both speech false alarm rates (Spearman $\boldsymbol{\rho}$;=0.91; p=2.56x10$^{-26}$) and clinical hallucination severity (Spearman $\boldsymbol{\rho}$;=0.41; p=6.98x10$^{-4}$). To explore the role of dopamine in these altered computations, we collected neuromelanin-sensitive (NM)-MRI, a validated proxy measure of nigrostriatal dopamine function, in a subset of patients (N=29). We found that hallucination severity (Spearman $\boldsymbol{\rho}$;=0.66; p=3.46x10$^{-4}$), speech false alarm rates (Spearman $\boldsymbol{\rho}$;=0.64; p=5.67x10$^{-4}$), and fitted values of the bias parameter (Spearman $\boldsymbol{\rho}$;=0.58; p=2.13x10$^{-3}$) correlated with NM-MRI signal in the substantia nigra. Our results are consistent with a model of hallucinations whereby excess nigrostriatal dopamine drives changes in perceptual processing and increases the probability of experiencing false percepts.

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**Topic:** H.13. Schizophrenia

**Support:** NIH R01 Grant MH114965
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**Title:** Examining a Neurobiological Psychosis Continuum via Neuromelanin-Sensitive MRI

**Authors: *A. FOGELSON**, A. VELIKOVSKAYA, B. ASHINOFF, K. WENGLER, A. MIHALI, M. A. BUTT, G. HORGA;
Columbia Univ., New York, NY

**Abstract:** Psychosis is a multifaceted syndrome characterized by perceptual, cognitive, and emotional disturbances in schizophrenia spectrum disorders. While research has shown that clinical symptoms of psychosis exist on a continuum—ranging from subclinical occurrences in the general population to clinically significant psychotic symptoms in clinical populations—additional scientific investigation is required to determine whether this continuum exists

neurobiologically. Understanding its existence could aid in more accurate diagnosis and prediction of psychosis conversion in at-risk groups. Previous studies have demonstrated a link between nigrostriatal dopamine function and psychosis in clinical groups. We therefore investigated a potential underlying neurobiological mechanism of this continuum by using neuromelanin-sensitive MRI (NM-MRI)—a novel proxy measure that captures hyperdopaminergic function in psychosis—to assess relationships with severity of clinical and subclinical psychosis-like symptoms. Our sample consisted of unmedicated individuals with schizophrenia (n=42), individuals at clinical high risk (CHR) for psychosis (n=53), and healthy controls (n=52). Severity of delusions and hallucinations were assessed using the Peters et al Delusions Inventory (PDI) and the Cardiff Anomalous Perceptions Scale (CAPS), respectively. NM-MRI data was acquired using an optimized 2D GRE-MT sequence. We first investigated relationships with average NM-MRI contrast within a region-of-interest in the ventral substantia nigra (SN) previously shown to relate to psychosis severity (Cassidy et al., 2020). While we found the expected correlation with PDI and CAPS in schizophrenia, we failed to detect a correlation across schizophrenia, CHR, and healthy individuals (PDI: r=0.04, p=0.64; CAPS: r=0.03, p=0.73). Results were similar for exploratory voxelwise analyses within the whole SN, which identified significant interactions of the relationship between NM-MRI contrast and psychosis-like experiences by group. We then identified a subset of items on the PDI and CAPS that were strongly correlated with clinician-measured psychosis severity in individuals with schizophrenia to better capture psychosis-relevant features; results held when using these items. Overall, these results do not provide evidence for a common relationship between NM-MRI contrast and psychosis existing on a continuum across healthy, subclinical, and clinical psychosis populations. While preliminary, this evidence may be more consistent with the notion of distinct neurobiological mechanisms driving psychosis-like symptoms across the clinical continuum.

**Disclosures:** **A. Fogelson:** None. **A. Velikovskaya:** None. **B. Ashinoff:** None. **K. Wengler:** None. **A. Mihali:** None. **M.A. Butt:** None. **G. Horga:** None.

**Poster**

**PSTR055. Behavior and Symptoms of Psychosis**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR055.13/VV26

**Topic:** H.13. Schizophrenia

**Support:** NIH Grant T32-MH018870
NIH Grant R01-MH114965
NIH Grant R01-MH117323

**Title:** The Neurofunctional Correlates of Prior Weighting in Belief Updating across the Schizophrenia Spectrum and Health

**Authors:** ***B. K. ASHINOFF**[1], K. WENGLER[2], N. M. SINGLETARY[3], N. OJEIL[4], G. HORGA[5];

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**Abstract:** Delusions are rigid, certain beliefs despite contradictory evidence. In sequential belief updating tasks, healthy individuals tend to underweight older information when forming new beliefs, leading to a recency bias. It's been shown that patients with delusions have a reduced recency bias, leading to more certain and rigid beliefs in a manner like delusions. Given this, we sought to identify where prior-weighted beliefs are represented in the brain across the schizophrenia spectrum and health. Our sample included 41 patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder, and 33 healthy controls. All reported analyses were conducted across the full sample of patients and controls (N = 74) as there were no significant differences between groups in these analyses. In an MRI scanner, subjects estimated the draw-by-draw probability that a box was filled with mostly blue or green beads based on 8 sequentially drawn samples from the box. The order of the sequences were systematically manipulated and an incentive-compatible belief-elicitation procedure was used. Across patients and controls, greater prior underweighting corresponded to stronger recency biases.To identify belief-updating neural signals, we conducted a first-level GLM using the draw-by-draw absolute logit posterior beliefs (based on reported probabilities) as a parametric modulator. ROIs were defined based on significant clusters from this analysis. We derived model-based draw-by-draw posterior beliefs using the fitted parameters from a Bayesian model with prior weighting. A first-level GLM analysis was conducted using the model-based absolute logit posterior beliefs as a parametric modulator. Only activation in a region within the paracingulate cortex correlated across the model-agnostic and model-based fMRI analyses, suggesting that this region represents prior-weighted posterior beliefs. For additional support, we fit a model with no prior weighting to subjects' data and analyzed the fMRI data based on the fitted absolute logit posterior beliefs. Formal model comparison favored the model with prior weighting specifically in the paracingulate-cortex region. Our results suggest that the paracingulate cortex represents prior-weighted posterior beliefs. Because there were no group differences in parametric modulation of the fMRI signal, these results suggest that the mechanisms underlying prior weighting may be similar in the schizophrenia spectrum and health. Future analyses will examine whether this region is involved in integrating priors and likelihoods and the connection between neural representations here and the severity of delusions.

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**Poster**

**PSTR055. Behavior and Symptoms of Psychosis**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR055.14/VV27

**Topic:** H.13. Schizophrenia

**Support:** R01MH117323
R01MH114965

**Title:** Introspective inference counteracts perceptual distortion

**Authors: *A. MIHALI**[1], C. MENDES DE LEON[3], A. VELIKOVSKAYA[2], A. FOGELSON[2], M. BROEKER[4], F. RAGALMUTO[2], G. HORGA[2];
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**Abstract:** Introspective agents can recognize the extent to which their internal subjective perceptual experiences deviate from the actual states of the external world. This ability, also known as insight, is critically required for reality testing and is impaired in psychosis, yet very little is known about its cognitive underpinnings. We developed a Bayesian modeling framework and a novel psychophysics paradigm to quantitatively characterize this type of insight. To induce strong perceptual distortions, we created a task based on a variant of the motion after-effect (MAE) illusion. Across two experiments with 44 healthy participants total, we asked people to report their subjective percepts ('See' condition) and used the implicit nulling method (Hiris and Blake, 1993) to quantify the strength of their MAE illusions. To measure insight in a quantitative manner, we quantified participants' ability to report beliefs in which they attempted to compensate for their perceptual distortions due to the MAE. When participants were required to infer the actual direction of motion ('Believe' condition), we found that people could compensate for the illusion. In a second experiment, a parametric choice of the test stimuli allowed us to apply our Bayesian model of perceptual insight to the participants' responses and confidence reports and found that it provided a good fit to the data (Mihali et al, 2022). This model revealed that a possible mechanism for belief compensation is incorporating knowledge of the perceptual distortion into the likelihood and thus the decision. Furthermore, confidence reports, reaction times and pupil dilation patterns shifted in tandem with the psychometric curves, suggesting changes in uncertainty during belief compensation and supporting an interpretation in terms of adjustments at an intermediate inference stage. An application of the drift diffusion model (Shinn et al, 2020) to the choice and reaction times data identified changes in drift rate and importantly the starting point in the "Believe" condition relative to the "See" condition, but no differences in the decision bound, thus ruling out a response-bias mechanism for compensation. In sum, we show that healthy individuals may plausibly perform insightful inference and compensate for internal distortions through adjustments in perceptual-decision variables.

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**Poster**

**PSTR055. Behavior and Symptoms of Psychosis**

**Location:** WCC Halls A-C

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**Topic:** H.13. Schizophrenia

**Support:** NIH Grant F32 MH125540
NIH Grant R01 MH117323
NIH Grant R01 MH114965

**Title:** Individual-level neural decoding of auditory verbal hallucinations from speech-selective cortex

**Authors: *K. WENGLER**[1], X. HE[1], J. BUCK[1], N. KRIEGESKORTE[2], G. HORGA[1];
[1]Psychiatry, [2]Columbia Univ., New York, NY

**Abstract:** Auditory verbal hallucinations (AVHs) are a quintessential symptom of psychosis that affects ~70% of patients with schizophrenia. AVHs cause significant distress and are viewed as emblematic of mental illness from a societal standpoint. Thus, understanding their neurobiological mechanisms could have disproportionate effects for destigmatizing these conditions. Modern methods for characterizing AVH-related patterns of neural activity and how they relate to speech-evoked patterns (e.g., MVPA, RSA) have yet to be applied to the study of AVHs. We used a speech discrimination paradigm with an fMRI clustered temporal acquisition. For each trial of the task, individuals were presented either a speech stimulus, a non-speech stimulus or no auditory stimulus, and were asked “Did you hear any voices?” AVH events were defined as reports of hearing voices on trials where no auditory stimulus was presented; blank events were defined as reports of not hearing voices on those trials. 59 unmedicated patients with schizophrenia completed the task—of those, 8 had sufficient AVH and blank events for decoding. First, for each subject, we defined individual speech-selective auditory cortex regions as voxels exhibiting the strongest differential responses to speech stimuli over non-speech stimuli. We then used MVPA within these regions to develop individual-level decoders for classifying AVH and blank events. We could successfully decode AVHs at the group level (mean accuracy = 56.7%, P = 0.001), with significant accuracy at the individual level in 4 subjects. A cross-classification analysis (train speech vs non-speech) was not able to successfully cross-classify AVH events in any of the 8 subjects, suggesting distinct activation patterns for speech and AVH events. To further characterize the distinctness of AVH and speech-evoked activation patterns, we performed RSA and found that AVH activation patterns were most similar to those for blank events, followed by non-speech events, and lastly speech events. A mediation analysis found that expression of AVH patterns mediated the relationship between speech expectations based on previous trial report and current trial report (path $axb$ = 40.45, $P$ = 0.013), suggesting that AVH patterns are related to the history of perceived speech and potentially facilitate a prior-dependent mechanism. Taken together, our results demonstrate an unambiguous role of speech-selective auditory cortex in the pathophysiology of AVH. They further place AVH activation patterns within the context of computational models of psychosis that posit a central role of enhanced context-dependent prior expectations in the generation of psychosis.

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**Poster**

**PSTR055. Behavior and Symptoms of Psychosis**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR055.16/VV29

**Topic:** H.13. Schizophrenia

**Support:** NIH Grant 1R01MH129395-01A1

**Title:** Developmental Patterns and Cognitive Relevance of Intrinsic Neural Timescales in Humans

**Authors: *I. E. ROSARIO**[1], A. T. GOLDBERG[1], S. LEE[1,2], K. WENGLER[1,2], G. HORGA[1,2]; [1]NYSPI, New York, NY; [2]Psychiatry, Columbia Univ., New York, NY

**Abstract:** Describing the normative developmental trajectories of neuroimaging phenotypes is a critical step toward contextualizing alterations in neuropsychiatric disorders. The resting-state fMRI measure of intrinsic neural timescale (INT) reflects the time window of neural integration and can serve as an index of excitation-inhibition balance (E/I) in cortical microcircuits. E/I is impacted in neuropsychiatric illness and is critical to cognitive functions such as working memory (WM). We have shown reduced INT in patients with schizophrenia (Wengler et al. 2020), but it remains unclear how these relate to neurodevelopment and WM deficits. INT maps were estimated as in our previous work in two large-scale neuroimaging datasets (55% female) from the Human Connectome Project: Development [HCP-D] (n = 591, 6–21 years old) and Young Adult [HCP-YA] (n = 1010, 22–37 years old). Developmental INT curves were calculated for each parcel using GLMs: INT = B0 + B1*age + B2*age$^2$ + B3*sex + B4*motion. Inflection points were calculated as the peaks of the fitted quadratic functions. The relationship with WM was evaluated in the HCP-YA sample by partial correlation between N-back performance and average INT in parcels significantly activated by the N-back task (contrast: 2-back > 0-back). Permutation tests were used to determine statistical significance and correct for multiple comparisons. Nearly all parcels showed significant age effects characterized by an inverted-U shape with an increase in INT across early childhood/adolescence and a decrease in INT in adulthood (age: 180/188 parcels positive effect, $P < 0.05$, $P_{FWE,permutation} = 0.001$; age2: 182/188 parcels negative effect, $P < 0.05$, $P_{FWE,permutation} = 0.001$). Inflection points ranged from ~21–36 years of age and occurred later in higher-order brain regions (Pearson $r = 0.75$, $P_{permutation} = 0.001$). Sex-stratified analysis showed that females had later inflection points than males (mean difference = 4.20 years, $t = 18.6$, $P_{permutation} = 0.001$). Results were robust to controls for motion. Critically subjects with better cognitive performance had longer INT in brain regions activated by the N-back task ($r = -0.09$, $P_{permutation} = 0.012$). Additional analyses include investigating effects with alternative hierarchies and relationships between developmental trajectories of cognition and INT. Our results describe an inverted-U-shaped age-related developmental patterns of INT and confirm the theoretical link between temporal integration windows at rest and the ability to maintain information in WM, supporting the potential value of INT for studying developmental cognitive dysfunction in neuropsychiatric illness.

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**Poster**

**PSTR055. Behavior and Symptoms of Psychosis**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR055.17/VV30

**Topic:** H.10. Human Learning and Cognition

**Support:** Deutsche Forschungsgemeinschaft (PE1627/8-1, Code 496990750)

**Title:** Higher-order perseveration behavior during reinforcement learning in volatile environments in recurrent neural networks and human learners

**Authors: *D. TUZSUS**[1], I. PAPPAS[2], J. PETERS[1];
[1]Univ. of Cologne, Cologne, Germany; [2]USC, Los Angeles, CA

**Abstract:** During decision-making in non-stationary environments (e.g. restless bandit problems often examined in reinforcement learning), human learners use a mixture of random and directed exploration (i.e. preferential sampling of options with information gain). Recurrent neural networks (RNNs), on the other hand, solve these problems using a combination of hyperperseveration and uncertainty avoidance. Informed by past work on human habit formation, we incoporated higher-order perseveration into an established bayesian learning model for restless bandit problems. The extended model decomposed perseveration behavior into a parameter reflecting the degree of temporal integration, and a standard perseveration bonus parameter. The extended model accounted for both human and RNN behavioral data better than previous models without high-order perseveration. Accounting for higher-order perseveration increased directed exploration effects in both human and RNN data. Furthermore, while the overall perseveration bonus was substantially larger in RNNs, human learners and RNN exhibited a similar degree of temporal intergration of their individual choice history. In contrast to our earlier work, accounting for hyperperseveration yielded positive (albeit numerically small) exploration bonus parameters in RNN behavior, suggesting the presence of a reliable but small directed exploration effect in RNNs. Findings highlight common mechanisms underlying perseveration and exploration behaviour in human learners and RNNs, and confirm that accounting for higher-order perseveration effects is crucial in the computational modeling of reinforcement learning tasks.

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**Poster**

**PSTR055. Behavior and Symptoms of Psychosis**

**Location:** WCC Halls A-C

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**Program #/Poster #:** PSTR055.18/Web Only

**Topic:** H.13. Schizophrenia

**Support:** the National Natural Science Foundation of China General Project (grant number: 32271138)
the Beijing Natural Science Foundation, China (grant number: 7202086)
the Science and Technology Program of Guangzhou, China (grant number: 202201011338)

**Title:** Brain Substrates Underlying the Association between Emotional Speech-in-Noise Recognition and Psychiatric Symptoms in Schizophrenia

**Authors:** S. SHE[1], Y. ZHENG[2], ***C. WU**[3];
[1]The Affiliated Brain Hosp. of Guangzhou Med. Univ., Guangzhou, China; [2]Guangzhou Brain Hosp., Guangzhou Med. Univ., Guangzhou, China; [3]Peking Univ. Hlth. Sci. Ctr., Beijing, China

**Abstract: Background** The speech-in-noise recognition (SR) and auditory emotion recognition deficits are associated with psychiatric symptoms in patients with schizophrenia (SCH). However, how the prosody embedded in target speech affects SR and relates to psychiatric symptoms in SCH remains unclear. This study examined the association of emotional SR with psychiatric symptoms and its neural mechanism in SCH. **Methods** The study was approved by the Medical Ethics Committee of Peking University (IRB00001052-21119). Fifty-four SCH and 59 healthy control participants (HCs) underwent the SR task (under the noise masking, the 12-character Chinese pseudo sentences were uttered in neutral, happy, sad, angry, fear, and disgust prosody; participants were asked to repeat the target sentences as accurately as possible), positive and negative syndrome scale (PANSS) assessment, and magnetic resonance imaging scanning. We used multivariate analyses of partial least squares (PLS) regression and mediation analyses to explore the associations among the six emotional SR, brain gray matter volume (GMV), and psychiatric symptoms. **Results** Negative prosody worsened SR and reduced SR changing rates. SCH had lower emotional SR and SR changing rates than HCs. Emotional SR was associated with acoustic features. A brain GMV (especially the association cortex, insula, cuneus, and cingulate cortex) component was associated with the anger, fear, and neutral SR in HCs and the disgust SR in SCH. The emotional SR component was associated with a psychiatric-symptoms profile (the negative syndrome, motor retardation, poor attention, conceptual disturbance, and poor insight), mediated by the brain GMV component (39.3% variances explained) in SCH. **Conclusions** The emotional SR abnormities and psychiatric symptoms are related via a GMV profile in the speech/emotion regions. The findings pave a potential way to improve psychiatric symptoms through the behavioral intervention of prosodic SR in schizophrenia.

**Disclosures: S. She:** None. **Y. Zheng:** None. **C. Wu:** None.

**Poster**

**PSTR055. Behavior and Symptoms of Psychosis**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR055.19/VV31

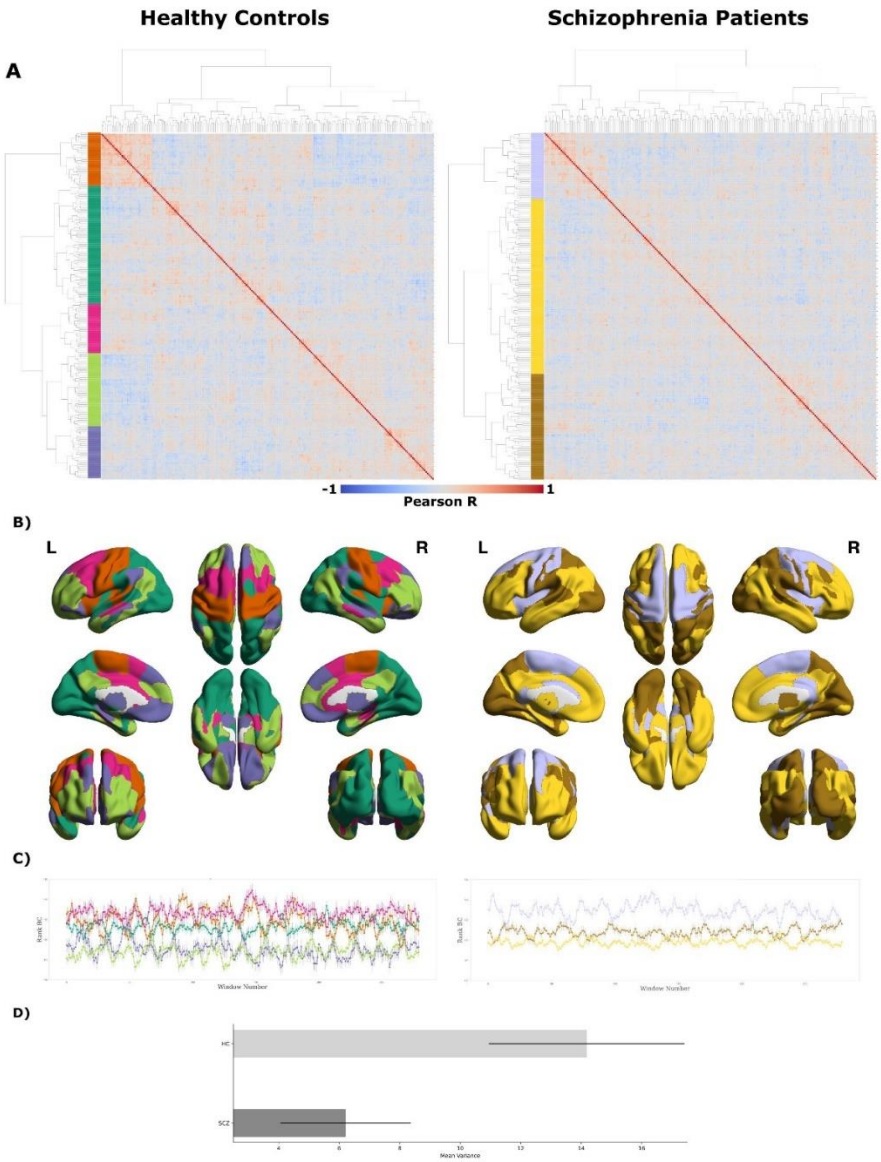
**Topic:** H.13. Schizophrenia

**Support:** NIH Grant MH111177

**Title:** The adaptive dynamics of the connectome in schizophrenia is disrupted during learning.

**Authors: *D. BHATT**, J. KOPCHICK, D. KHATIB, P. THOMAS, U. RAJAN, C. ZAJAC–BENITEZ, L. HADDAD, A. AMIRSADRI, J. A. STANLEY, V. A. DIWADKAR;
Wayne State Univ., Detroit, MI

**Abstract:** Learning-induced neuroplasticity alters the dynamics of the brain's connectome (Meram et al., 2023), but network inflexibility and altered neuroplasticity in schizophrenia (SCZ) may impair network dynamics. Here dynamic functional connectivity (DFC) using an established moving window technique was applied to fMRI signals (Siemens Verio 3T) acquired during an established learning task (Hasan et al., 2023)(n=88; 49 SCZ). In each participant, first, a full undirected functional connectivity matrix in a 246-region cerebral space (Fan et al., 2016) was estimated in 280 successive and partially overlapping moving windows (window width of 9 images). Treating each matrix as an undirected graph, we computed the betweenness centrality (BC) of each of the 246 nodes (before rank ordering nodes in each window) (Brandes, 2001). Thus, across the width of the task, the 280-point time series of BC ranks for any node, captures its dynamic role in the network. Across all subjects in each group, a "connectivity" matrix of node dynamics was derived by first averaging the time series of BC ranks, before computing the correlation of these time series across all pairs of nodes. Then, within each group (HC, SCZ), these matrices were submitted for agglomerative hierarchical clustering (Varoquaux et al., 2015). Two distinct cluster solutions were observed (Figure 1), with five distinct clusters identified in HC and three in SCZ. The locations of the nodes in these unique clusters were mapped to the cerebral surfaces, and the BC time series of all nodes within each cluster was created. The variance of each of the cluster's time series was used as a surrogate measure of "flexibility" (higher variance = more flexible); as seen, SCZ was characterized by substantially lower flexibility. The analytical pipeline and our cumulative results emphasize the importance of understanding altered task-driven network dynamics in schizophrenia.




A) The hierarchical agglomerative clustering solutions are depicted for each of the HC and SCZ (the number of clusters was determined based on the Within-Cluster Sum of Squares (elbow) plot and the threshold vs. number of clusters plot). The solution identified five clusters in HC and three in SCZ (distinguished by unique colors on the adjoining vertical axis) with the color bar (bottom) indicating the direction of the correlation (negative: blue; positive: red). B) The locations of the nodes in these unique clusters were mapped to the cerebral surfaces (the color code is maintained in each of the HC and SCZ groups), yielding clearly differentiable networks (more closely mapped to the structural anatomy in HC). C) Next, to investigate the "flexibility" of the discovered clusters/networks, first average BC time series of all nodes assigned to the clusters were computed (again the color scheme remains consistent)(error bars are ± sem). D) Finally, the variance of each of the time series was used

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**Poster**

**PSTR055. Behavior and Symptoms of Psychosis**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR055.20

**Topic:** H.10. Human Learning and Cognition

**Support:** IDEXLYON - IMPULSION

**Title:** Adaptability of the sense of agency when playing (without knowing it) against oneself

**Authors:** M. TOMA[1], J. MATTOUT[2], R. QUENTIN[3], F. RASSOULOU[4], E. MABY[2], ***M. VERNET**[5];
[1]CRNL-Impact, Bron, France; [2]CRNL - Cophy, Bron, France; [3]CRNL - Eduwell, Bron, France; [4]Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany; [5]CNRS / CRNL-Impact, Bron, France

**Abstract:** The sense of agency (SoA) is the subjective feeling that we are at the origin of our own volitional actions and of their consequences in the world. It is central to fluency of action, responsibility and wellbeing in humans. It can be degraded in neuropsychiatric patients but also in healthy populations interacting with technologies when consequences of actions are delayed from the actions. Human beings are constantly exposed to such delays in everyday life and have partially adapted their SoA to such situations. In the present study, we aimed to observe early SoA adaptation mechanisms. For this, we exposed humans to an unprecedented situation, where the consequence of an action literally preceded the action itself.
A group of 112 healthy participants (55 females; 14 left-handed; 27±7 years old) played an online game where they had to find a visual target in a grid of distractors. Once they found it, they pressed a button and then made a rapid and straight movement with the mouse to bring the cursor over the target and click on it, which triggered an animation. After a short training, an algorithm predicted the time of the participants' click based on past and current movements and triggered the animation before the click (on average 78±20µs before the click). The participants, who believed they played against the computer, reported whether they clicked first (SoA=1) or whether the computer won (SoA=0) in 6 blocks of 80 trials (lasting in total 45-60 min). One participant was excluded because she always reported winning.
The results show that the SoA increased over the course of the game, from on average 66±17% in the first block to 79±17% in the last. The partial correlation between blocks and SoA, controlled for the timing between animation's start and participants' click, was significant ($r=0.14$, $p<0.001$).
According to the temporal order of events, the computer always triggered the animation. However, according to a causal point of view, the participants triggered it. Indeed, the consequence's timing was not randomly controlled by the algorithm, but rather based on past and current movements of the cursor in order to trigger the animation before the participant's click. The impact of these opposite realities was an increasing SoA over the course of the experiment. Thus, the participants implicitly learned, despite the unusual timing, that they were at the origin of the animation and adapted their SoA accordingly. By reversing the timeline of action and consequence, we were thus able to observe the dynamics of the adaptability of the sense of agency.

**Disclosures:** **M. Toma:** None. **J. Mattout:** None. **R. Quentin:** None. **F. Rassoulou:** None. **E. Maby:** None. **M. Vernet:** None.

**Poster**

**PSTR055. Behavior and Symptoms of Psychosis**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR055.21/VV32

**Topic:** H.10. Human Learning and Cognition

**Support:** GRF Grant 17612222
RFS2021-7H05

**Title:** Discrete Neural Mechanisms Underpinning the Encoding of Certain and Uncertain Inputs During Visual Statistical Learning

**Authors:** ***P. ZHANG**, X. S. TONG;
The Univ. of Hong Kong, Hong Kong, Hong Kong

**Abstract:** Increasing evidence shows that humans can involuntarily acquire associative patterns through statistical properties embedded in the environmental input. Two accounts have been proposed, with one emphasizing the adapted neural processing elicited by the high-probable (high-certainty) events, while the other suggests that the enhanced neural responses evoked by low-probable (high-uncertainty) events reflect the update of belief based on new observations. However, the question of how the neural mechanisms underlying the adaptation of certainty and the coping of uncertainty are operated during statistical learning remains unexplored. This study employed electroencephalography (EEG) to examine the oscillatory responses evoked by associative objects (i.e., probabilistic cues) when inputs (i.e., targets) appeared with different likelihoods. During a visual statistical learning paradigm, targets appeared after specific cues at high- (75%) or low- (25%) probability, which induced certainty or uncertainty, respectively. Following these targets, cue objects appeared again and were classified as high- (75%), low- (25%), and zero-associated based on the possibilities of showing ahead of that target. Time-frequency analysis revealed the desynchronization in alpha/beta (10-25 Hz) frequency band across frontal to occipital regions, with attenuating effects on the high-associated cues after the appearance of high-probable targets. In addition, the synchronization in theta (4-10 Hz) frequency band was observed in the fronto-central region with enhanced power on high-associated cues after encountering low-probable targets. Moreover, in parieto-occipital and occipital regions, the theta synchronization elicited by low-associated cues was reduced when these cues appeared after low- compared to high-probable targets. These results suggest that the neural mechanisms underlying the adaptation of certainty and minimization of uncertainty during statistical learning might be disassociated: The sensory inputs occurring with higher certainty trigger a global cortical adaptation for reliable associations, while the inputs arising uncertainty might lead to retrieval of reliable associations but attenuated visual processing of unreliable ones.

**Disclosures:** **P. Zhang:** None. **X.S. Tong:** None.

**Poster**

**PSTR055. Behavior and Symptoms of Psychosis**

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**Topic:** H.13. Schizophrenia

**Support:** Recherche du Québec—Nature et technologies Grant 2014-PR-171935

**Title:** Unlocking the cognitive potential of individuals with schizotypal traits using a social role task

**Authors:** ***M. DIAO**[1], I. DEMCHENKO[2], G. ASARE[2], J. QUAN[2], J. DEBRUILLE[2];
[1]McGill Univ. Integrated Program in Neurosci., Montreal, QC, Canada; [2]McGill Univ., Montreal, QC, Canada

**Abstract:** Schizophrenia (Sz) patients make more errors and take longer times to respond than healthy controls in most cognitive tasks. Deficits are also observed, though to a lesser extent, in subclinical participants having high scores at the schizotypal personality questionnaire (the SPQ). They are accompanied by smaller amplitudes of the event-related brain potentials (ERPs) that index attention, working memory and storage in episodic (declarative) memory. These functions are thus thought to be impaired in people having schizophrenia attributes (SzAs). Nevertheless, an absence of longer response times was recently found in high SPQ participants during a task using names of social roles as stimuli and including many extraordinary favorable and unfavorable ones (e.g., superhero & persecutor). This task required participants to decide, as quickly and as accurately as possible, whether or not they could consider performing the role at any moment of their lives. To further test an absence of cognitive deficits in this task, the ERPs elicited by hundreds of names of social roles were recorded in one hundred and seventy-five healthy participants aged 18 to 33. The absence of longer reaction times in high- (1038 ms) than in low-SPQ participants (1024 ms) was replicated. Moreover, the ERPs of high-SPQ participants included significantly larger occipital N1s ($p = .023$) and larger P2s ($p = .004$) than low-SPQ participants while their N400 and LPPs were of similar amplitudes. These findings suggest that the social role task was attractive enough for the high SPQ participants to engage in the experiment, allocate their attention and involve their selves in the task without cognitive anomalies. Such surprising results are in fact consistent with clinical observations of a greater attention to, and a faster processing of, stimuli that can be related to extraordinary-or-delusional ideations-or-beliefs. This indicates that the cognitive impairments of people with SzAs may not be pervasive but rather selective, affecting certain areas while leaving others relatively intact. Further studies are thus needed to test whether the cognitive deficits found in SzAs could be due to the use of tasks and stimuli that are less within their focus of interest than within that of healthy controls.

**Disclosures:** **M. Diao:** None. **I. Demchenko:** None. **G. Asare:** None. **J. Quan:** None. **J. Debruille:** None.

**Poster**

**PSTR056. Electrophysiology Techniques: Methods for Multicellular Recording In Vitro and In Vivo**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR056.01/VV34

**Topic:** I.04. Physiological Methods

**Title:** Label-free functional analysis for the characterization of iPSC-derived neural organoid development and maturation

**Authors:** D. SULLIVAN, B. STREETER, P. ELLINGSON, ***A. P. PASSARO**, S. A. CHVATAL, D. MILLARD;
Axion BioSystems, Atlanta, GA

**Abstract:** The flexibility and accessibility of induced pluripotent stem cell (iPSC) technology has allowed complex human biology to be reproduced in vitro at high throughput scales. Indeed, rapid advances in stem cell technology have led to widespread adoption for the development of in vitro models of neuron electrophysiology to be used in screening applications in drug discovery and safety. Furthermore, advanced cell preparations, such as spheroids or organoids, are under intense investigation with aims toward establishing mature human phenotypes in vitro. The objective of this work is to develop and validate a live-cell analysis workflow for the characterization of neural organoids in vitro. First, whole-vessel live-cell imaging was used to monitor iPSC colony formation and expansion in real-time. iPSCs were consistently passaged according to readouts of colony size and coverage. In addition, imaging was used to track the size and shape of embryoid body formation and the induction of neural differentiation. At day 50+, organoids were transferred to a multiwell microelectrode array plate and allowed to attach. A planar grid of microelectrodes embedded in the substrate of each well of the culture plate interfaced with cultured neural organoids. Impedance measurements were used to quantify the attachment of the organoids to the substrate and microelectrodes, as a measure of cell viability and electrode coverage. Broadband (1 - 5000 Hz) electrophysiological data was acquired and then separately processed for action potential detection (200 - 5000 Hz) and low frequency oscillations (1 - 50 Hz). The power spectral density was computed from the low frequency signal sampled after network burst events, and then absolute power was computed in the delta (1-4 Hz), theta (4-8 Hz), alpha (8-14 Hz), beta (14-30 Hz), and gamma (30-50 Hz) bands. The emergence and maturation of neural organoid electrophysiological activity was tracked via these measurements of spiking activity and low frequency oscillations, coupled with the long-term monitoring of size via live-cell imaging. These results support the continued development of in vitro 3D models of neural function.

**Disclosures:** **D. Sullivan:** A. Employment/Salary (full or part-time); Axion BioSystems. **B. Streeter:** A. Employment/Salary (full or part-time); Axion BioSystems. **P. Ellingson:** A. Employment/Salary (full or part-time); Axion BioSystems. **A.P. Passaro:** A. Employment/Salary (full or part-time); Axion BioSystems. **S.A. Chvatal:** A. Employment/Salary (full or part-time); Axion BioSystems. **D. Millard:** A. Employment/Salary (full or part-time); Axion BioSystems.

**Poster**

**PSTR056. Electrophysiology Techniques: Methods for Multicellular Recording In Vitro and In Vivo**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR056.02/VV35

**Topic:** B.06. Intrinsic Membrane Properties, Electrical Synapses, and Signal Integration

**Title:** High density MEA recording of primary rat neuron cultures and human iPSC-derived neuron cultures growing at low density on astrocyte feeder layers

**Authors: *C. TIAN**, C. M. PETROSKI, D. LIU, A. E. SNYDER, P. J. GANDHI, R. E. PETROSKI;
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**Abstract:** Primary rodent neuronal cell cultures are used for both mechanism of action studies and validation of gene targets expressed in their native environment. Drug discovery projects rely on primary rodent neuronal cell cultures to interrogate the efficacy and potency of novel therapeutic molecules. Functional electrophysiological properties of neurons measured are by patch clamp recording. Neurons growing at low density on a monolayer of astrocytes are an ideal model system for developing the mature neuronal phenotype *in vitro*. Astrocytes provide the optimum substrate for neuronal survival and differentiation. Neurons express a full repertoire of voltage-gated and ligand-gated ion channels as well as GPCRs that modulate neuronal excitability. Both intrinsic and synaptic excitability can be recorded in these cultures. However, the data throughput of patch clamp recording is limited to 1 or 2 neurons at a time. High density microelectrode arrays (MEAs) from MaxWell promise to greatly increase the data throughput of functional endpoints to 100s to 1,000s of neurons at a time. Conventionally, MEA data has been generated from neuronal cultures plated at very high density (2,000-3,000 cells/mm2). We present MEA data recorded from low density rat cortical neuron cultures (25-100 cells/mm2) plated on astrocytes. These cultures conditions more closely resemble the conditions used for patch clamp recording. Neuronal activity (number of active electrodes, firing rate, bursting) increase with development time *in vitro*. In addition, we also present data from human iPSC derived NGN2 neurons at low density on a substrate of rat astrocytes.

**Disclosures:** **C. Tian:** A. Employment/Salary (full or part-time); Neuroservices-Alliance. **C.M. Petroski:** A. Employment/Salary (full or part-time); Neuroservices-Alliance. **D. Liu:** A. Employment/Salary (full or part-time); Neuroservices-Alliance. **A.E. Snyder:** A.

Employment/Salary (full or part-time); Neuroservices-Alliance. **P.J. Gandhi:** A. Employment/Salary (full or part-time); Neuroservices-Alliance. **R.E. Petroski:** A. Employment/Salary (full or part-time); Neuroservices-Alliance.

**Poster**

**PSTR056. Electrophysiology Techniques: Methods for Multicellular Recording In Vitro and In Vivo**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR056.03/VV36

**Topic:** I.04. Physiological Methods

**Support:** NEUREKA project, GA 863245, within the H2020 Framework Program of the European Commission.
HyVIS project, GA 964468, within the H2020 Framework Program of the European Commission.

**Title:** Next-generation electrophysiology for functional characterization of human neural organoids

**Authors: *L. D'IGNAZIO**, E. GUELLA, Z. LI, M. DE GENNARO, M. OBIEN; MaxWell Biosystems AG, Zurich, Switzerland

**Abstract:** The human brain is inaccessible to direct optical observation and experimental manipulation, and thus challenging to study. However, in recent years, human induced pluripotent stem cell (hiPSC)-derived brain models have become a fundamental tool for studying common neurological disorders, such as epilepsy, Alzheimer's disease, and Parkinson's disease. The ability to measure the electrical activity of a self-organizing *in vitro* cellular model in real time, live and label-free can provide much needed insights into the complexity of its neuronal network. High-density microelectrode arrays (HD-MEAs) provide unprecedented means for non-invasive *in vitro* electrophysiological recordings, and can be used to acquire measurements from any electrogenic sample, such as iPSC-derived neurons, retina explants, brain slices and neural organoids. In this study, we used the highest density MEA platform available (MaxWell Biosystems AG, Switzerland), featuring 26,400 electrodes per well, to capture extracellular action potentials in neural organoids at different scales, ranging from cell population networks to single-cell resolution and subcellular level, with high spatio-temporal resolution and low noise. We showcase the advantages of MaxWell Biosystems' HD-MEA system allowing for flexible selection of 26,400 electrodes for both recording and electrical stimulation, significantly increasing the reproducibility and the statistical power of the data collected from hiPSC-derived neural organoids over multiple weeks. Metrics such as firing rate, spike amplitude, and network burst profile were extrapolated in a parallelized manner, capturing even the smallest neuronal signals. Furthermore, we characterized the axonal function and structure of hiPSC-derived neural organoids using the AxonTracking Assay, a tool for automated recording and analysis of action potential conduction along individual axonal arbors of multiple neurons in parallel. The

AxonTracking Assay enables the measurement of action potential's conduction velocity and latency as well as axonal length, and number of axonal branches. This unique assay can be used to characterize disease models targeting the axon initial segment, axonal branching, development, and conduction at high-throughput. MaxWell Biosystems HD-MEA platforms, together with the automatically generated plots and extracted metrics, provide a powerful user-friendly approach to identify and isolate functionally active areas of a 3D culture in acute recordings and/or longitudinal studies, allowing for long-term *in vitro* disease modelling and compound testing.

**Disclosures: L. D'Ignazio:** None. **E. Guella:** None. **Z. Li:** None. **M. De Gennaro:** None. **M. Obien:** None.

**Poster**

**PSTR056. Electrophysiology Techniques: Methods for Multicellular Recording In Vitro and In Vivo**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR056.04/VV37

**Topic:** I.04. Physiological Methods

**Title:** Thermal modulation of spontaneous neuronal network activity in vitro

**Authors: A. S. CARRIZALES**, *P. SKELTON, I. M. BERKE, L. V. FORTUNO, A. DILEONARDI;
United States Army Res. Lab., Aberdeen, MD

**Abstract:** Physiological temperature is tightly controlled, and minor deviations can elicit a wide range of effects on cellular function. We therefore investigated how spontaneous neural activity is affected by hypo- and hyperthermic conditions. We cultivated networks of primary rat hippocampal neurons on glass micro-electrode arrays (gMEAs) and transduced the cultures with a genetically encoded calcium indicator (AAV1-hSyn1-GCaMP6s-P2A-nls-dTomato). This system allowed simultaneous evaluation of the activity of a single culture using both extracellular electrodes and optical measurements of calcium transients while temperature was modulated using a stage-mounted temperature controller. Two different temperature ramps were implemented: one in which temperature was reduced from physiological baseline (37°C to 29°C and then gradually increased to 43°C, and one in which temperature was initially increased from physiological baseline to 43°C before being gradually reduced). Spontaneous activity was recorded at 29, 34, 37, 41, and 43°C since previous reports have shown attenuation of population spikes at hypothermic temperatures, while temperatures above 40°C have been shown to initiate neurodegeneration. Moderate hypothermic temperatures (34°C) caused large sporadic bursts of activity, while stronger hypothermic conditions reduced neural firing. Both of the hyperthermic temperatures reduced spontaneous activity. Following each of the temperature ramps, the spontaneous network activity returned upon restoration of physiological temperature. Broadly, the calcium and electrophysiological data were in agreement. Ongoing work will aim to

determine whether calcium imaging and extracellular electrophysiology give similar results in more advanced analyses such as synchronicity and cross-correlation between individual neurons.

**Disclosures:** **A.S. Carrizales:** None. **P. Skelton:** None. **I.M. Berke:** None. **L.V. Fortuno:** None. **A. DiLeonardi:** None.

**Poster**

**PSTR056. Electrophysiology Techniques: Methods for Multicellular Recording In Vitro and In Vivo**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR056.05/VV38

**Topic:** I.04. Physiological Methods

**Title:** Establishing and assessing temporal interference electrical stimulation in neuronal cultures in vitro.

**Authors: *A. AHTIAINEN**[1], L. LEYDOLPH[2], J. TANSKANEN[1], A. HUNOLD[2,3], J. HAUEISEN[2], J. HYTTINEN[1];
[1]Fac. of Med. and Hlth. Technol., Tampere Univ., Tampere, Finland; [2]Inst. of Biomed. Engin. and Informatics, Technische Univ. Ilmenau, Ilmenau, Germany; [3]neuroConn GmbH, Ilmenau, Germany

**Abstract:** Electrical stimulation (ES) techniques, such as deep brain and transcranial electrical stimulation, have shown promise in alleviating the symptoms of depression and other neurological disorders *in vivo*. A novel noninvasive ES method, called temporal interference stimulation (TIS), shows great potential as it can be used to steer the stimulation and selectively activate different brain regions [1,2]. However, TIS and its effects on neuronal electrical activity have not been demonstrated *in vitro*. To address this, we established an *in vitro* setup for TIS on microelectrode arrays (MEA) using the MEA2100 system (Multi Channel Systems MCS GmbH) in combination with the neuroConn DC Stimulator MC (neuroConn GmbH). The stimulus was applied via four platinum electrodes that were submerged in the cell medium through a 3D-printed cap. Cultures of rat cortical neurons [3] at 28 days *in vitro* (DIV) were subjected to two channel stimulation with 1) TIS at 653 Hz and 643 Hz resulting in a 10 Hz frequency envelope, 2) low-frequency stimulation (LFS) at 10 Hz, 3) high-frequency stimulation (HFS) at 653 Hz, and 4) no ES (control) (n=4 MEAs/condition; stimulation: 450 µA for 5 minutes). We successfully established a novel stimulation platform for noninvasive ES of neurons *in vitro* with TIS characteristics. As hypothesized, HFS had no significant effect on neuronal activity. However, the TIS with a 10 Hz amplitude envelope elicited neuronal electrophysiological responses alike the LFS. These findings provide an understanding of the electrical modulation of neurons during TIS and valuable insights into the clinical applicability of TIS in treating various brain disorders.
[1] Grossman, N et al. Noninvasive Deep Brain Stimulation via Temporally Interfering Electric Fields. *Cell.* 2017;*169(6)*:1029-1041.e16. doi: 10.1016/j.cell.2017.05.024.

[2] Hunold, A et al. Review of individualized current flow modeling studies for transcranial electrical stimulation. *J Neurosci Res.* 2023;*101(4)*:405-423. doi: 10.1002/jnr.25154.
[3] Ahtiainen, A et al. Ketamine reduces electrophysiological network activity in cortical neuron cultures already at sub-micromolar concentrations - Impact on TrkB-ERK1/2 signaling. *Neuropharmacology.* 2023;*229*:109481. doi: 10.1016/j.neuropharm.2023.109481.

**Disclosures:** **A. Ahtiainen:** None. **L. Leydolph:** None. **J. Tanskanen:** None. **A. Hunold:** A. Employment/Salary (full or part-time); neuroConn GmbH. **J. Haueisen:** None. **J. Hyttinen:** None.

**Poster**

**PSTR056. Electrophysiology Techniques: Methods for Multicellular Recording In Vitro and In Vivo**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR056.06/VV39

**Topic:** I.04. Physiological Methods

**Support:** the National Research Foundation of Korea (NRF-2022R1I1A4063209)
the National Research Foundation of Korea (NRF-2022R1A2C2005062)

**Title:** High Density Cochlear Implant Electrode Arrays for Rodents

**Authors:** ***J. SOHN**[1], Y. LEE[2], S. JUN[2];
[1]Ewha Women's Univ., Seoul, Korea, Republic of; [2]Ewha Womans Univ., Seoul, Korea, Republic of

**Abstract:** Cochlear implants (CIs) are neural prosthetics that stimulate the ganglion cells in the auditory system to help people with hearing loss. Recently, it is reported that hearing loss is the most significant modifiable factor for dementia. Even though there were attempts to investigate the underlying mechanism of hearing loss-induced dementia, it is challenging to perform preclinical studies for cochlear implantation especially with rodents due to its small size. Most of precious studies with rodent CIs utilized only 3 to 8 channels, which are too small for sound restoration. Accordingly, in order to use intracochlear electrode arrays with the increased number of channels, we created a 10-channel intracochlear electrode for rodents. The electrode array is 15 mm in length. The distance between the electrodes is 0.3 mm, and each electrode is 0.25 mm long. The electrode's tip width is 0.2 mm. The electrodes were fabricated on a silicon wafer and PDMS. Wire arrays are made of platinum-iridium alloy foil. After CI surgery, the rat was stimulated while it was moving in the cage. We measured the electrical auditory brainstem response (EABR) when CI stimulation was delivered. As a result, it was verified that each of the 10 channels are functional. In future research, we will look into the effect of CIs on the cognitive function.

**Disclosures:** **J. Sohn:** None. **Y. Lee:** None. **S. Jun:** None.

**Poster**

**PSTR056. Electrophysiology Techniques: Methods for Multicellular Recording In Vitro and In Vivo**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR056.07/VV40

**Topic:** I.04. Physiological Methods

**Support:** National Taipei University of Technology-Penn State Collaborative Seed Grant (NTUT-PSU-112-01)

**Title:** Porous neural electrodes for tracking of brain & spinal cord neural activities with single cell resolution

**Authors: *T. ZHOU**;
Penn State Univ. Penn State Ctr. for Neural Engin., University Park, PA

**Abstract:** Mapping and modulating the neural network with cellular resolution could influence research into important neuroscience questions such as how existing neurons transform into neural circuits with diverse dynamics through learning and development. In addition, these developments could enhance brain-machine interfaces (BMIs) by facilitating reliable decoding from individual neurons as opposed to ensemble averages of large population activities for prosthetic applications. Furthermore, stable mapping and modulation could facilitate longitudinal, as opposed to cross-sectional, investigations of aging-related brain changes and neurodegenerative disease-induced cognitive decline. While most existing neural probes suffer from tissue-probe mechanical mismatch that results in glial scar formation at the tissue probe interface, we have developed a porous neural electrode that can provide matching mechanical properties with the neural tissue. It is porous and has micrometer-scale feature sizes, which provides its favorable mechanical and structural properties. This novel neural probe can provide stable tracking of neuron activities in both the brain and spinal cord of C56BL/6 mice. Both local field potentials (LFPs) and single neural spikes were recorded from the implanted porous neural electrodes. Unlike conventional rigid electrodes that show drifting in recording signals, the porous neural electrodes showed no obvious drifting in recording or loss of recorded signals. This is a breakthrough that can benefit many of the neuroscience research that involves electrophysiology studies.

**Disclosures: T. Zhou:** None.

**Poster**

**PSTR056. Electrophysiology Techniques: Methods for Multicellular Recording In Vitro and In Vivo**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR056.08/VV41

**Topic:** I.04. Physiological Methods

**Title:** Unraveling the functional significance of spinal neural activity during freely moving locomotion

**Authors: *N. SEVILLA**[1], Y. WU[2,3], B. TEMPLE[4], J. ZHANG[2,3], H. ZHU[2,3], P. ZOLOTAVIN[2,3], Y. JIN[2,3], D. DUARTE[5], E. SANDERS[6], E. AZIM[6], A. NIMMERJAHN[5], S. L. PFAFF[4], L. LUAN[2,1,3], C. XIE[2,1,3];
[1]Bioengineering, [2]Electrical and Computer Engin., [3]Neuroengineering Initiative, Rice Univ., Houston, TX; [4]Gene Expression Lab., [5]Waitt Advanced Biophotonics Ctr., [6]Mol. Neurobio. Lab., Salk Inst. for Biol. Studies, La Jolla, CA

**Abstract:** Recording the electrophysiological activity of neurons through implanted electrodes in nervous tissues is widely recognized as a fundamental approach to understanding their functions and circuits. However, in the case of the spinal cord, such neural recordings are primarily restricted to ex-vivo conditions or animals that are anesthetized and constrained. The spinal cord is highly mobile during behaviors, making it difficult for rigid electrodes to maintain contact, thereby resulting in noise, position drift, and degraded recording quality. Consequently, the scientific community faces obstacles in conducting mechanistic studies on the dynamic processing of motion and sensation in the spinal cord. Our recent study presents compelling evidence showcasing the capabilities of ultraflexible nanoelectronic thread (NET) electrodes in intraspinally recording neuronal populations in actively moving mice for acute and chronic periods. We designed and fabricated a 32-channel NET electrode (1.1 μm thickness) for the mouse spinal cord and developed surgical protocols for chronic intraspinal implantation. In awake, unrestrained moving mice, we successfully recorded extracellular action potentials free from motion artifacts. Our recordings showcased remarkable qualities such as a high signal-to-noise ratio, well-isolated clusters, and a representation of diverse functions related to locomotion. Our results demonstrate that NETs resolved a large number of single units in freely behaving mice (n=12), with unit amplitudes ranging from 50 μV to 400 μV. The quality metrics indicated low inter-spike interval (ISI) violations at 2ms, a high signal-to-noise ratio (>10), and high isolation scores (>0.9) across most animals. Additionally, the diverse range of waveform shapes and characteristics emphasized the highly varied nature of spinal cord neurons. A closer look at neural activity during varying motion speeds, we revealed a subset of recorded neurons that exhibited firing patterns strongly correlated with hindlimb locomotion. Furthermore, we investigated the stability of NET chronic recordings over 7 days in task performing animals and show we could track neuron populations consistently with an estimated 90% of units experiencing a daily drift of ± 13 μm. As a result, NETs allow for the longitudinal evaluation of the functional tunings of neurons. Multiple laboratories have independently validated this technology. By enabling real-time, high-fidelity measurements of single spinal neurons and neuronal populations during natural behaviors, NETs may pave the way to advance our fundamental understanding of spinal cord neurophysiology.

**Disclosures:** **N. Sevilla:** None. **Y. Wu:** None. **B. Temple:** None. **J. Zhang:** None. **H. Zhu:** None. **P. Zolotavin:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual

property rights/patent holder, excluding diversified mutual funds); Scientific consultant for Neuralthread, Inc. **Y. Jin:** None. **D. Duarte:** None. **E. Sanders:** None. **E. Azim:** None. **A. Nimmerjahn:** None. **S.L. Pfaff:** None. **L. Luan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-inventors on patent filed by The University of Texas on ultraflexible neural electrode technology used in the study and hold equity ownership in Neuralthread, Inc. **C. Xie:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-inventors on patent filed by The University of Texas on ultraflexible neural electrode technology used in the study and hold equity ownership in Neuralthread, Inc.

**Poster**

**PSTR056. Electrophysiology Techniques: Methods for Multicellular Recording In Vitro and In Vivo**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR056.09/VV42

**Topic:** I.04. Physiological Methods

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National Science and Technology Innovation 2021ZD0202202
Shanghai Municipal Science and Technology Major Project 2021SHZDZX
Shanghai Pujiang Program 21PJ1414400
National Natural Science Foundation of China 32200917

**Title:** Decoding mice hindlimb movement via spinal cord spike and local field potential activities recorded with a dense hyperflexible electrode

**Authors: *X. LI**[1,2], P. WANG[2], J. FAN[3], X. LI[2];
[1]Chinese Acad. of Sci., Shanghai, China; [2]Institue of neuroscience, Chinese Acad. of Sci. Ctr. for Excellence in Brain Sci. and Intelligence Technology, CAS., Shanghai, China; [3]Ctr. for Excellence in Brain Sci. and Intelligence Technol., Shanghai, China

**Abstract:** The spinal cord (SC) plays a vital role in motor control. However, revealing the electrical mechanisms underlying SC-mediated movement is limited by challenges in SC recording, such as the inherent movement of the SC causing signal loss.
To overcome this obstacle, we developed a 128-channel hyperflexible SC electrode for investigating SC-level electrical activity. Two male mice were trained to run on a wheel, and the probe was implanted in the L3 ventral horn post-training. SC signals were recorded at 20kHz, with movement captured at 60 fps. Joint movement was labeled using DeepLabCut. Data processing method included common median reference, filtering, and spike detection to extract spike and local field potential (LFP). Spike counts and LFP moving averages were computed using a 50ms sliding window and aligned with behavior. LSTM regression models were trained

with a 300ms time shift on ten recording sessions (8:1:1 split). Mean coefficient of determination ($R^2$) was calculated from 5 repeats. Results showed both spike and LFP effectively decoded joint movement with performance variations across signal types. One-way ANOVA indicated no significant difference between spike, 1-4Hz, and 4-8Hz LFP. Spike and low-frequency LFP outperformed high-frequency LFP. Principal component analysis revealed distinct neural trajectory patterns (circles, saddles, knots) in spike and low-frequency LFP during step cycles, while high-frequency LFP did not exhibit such patterns. Our results suggest a strong association between hindlimb rhythmic movement and SC spike, as well as low-frequency LFP.
In conclusion, our study offers valuable insights into the electrical characteristics of movement in the SC and presents novel findings on neural trajectories of intraspinal signals in moving mice. Furthermore, our study demonstrated the reliability of the hyperflexible SC electrode for in-vivo recording, paving the way for its potential as a transformative methodology in spinal cord research.

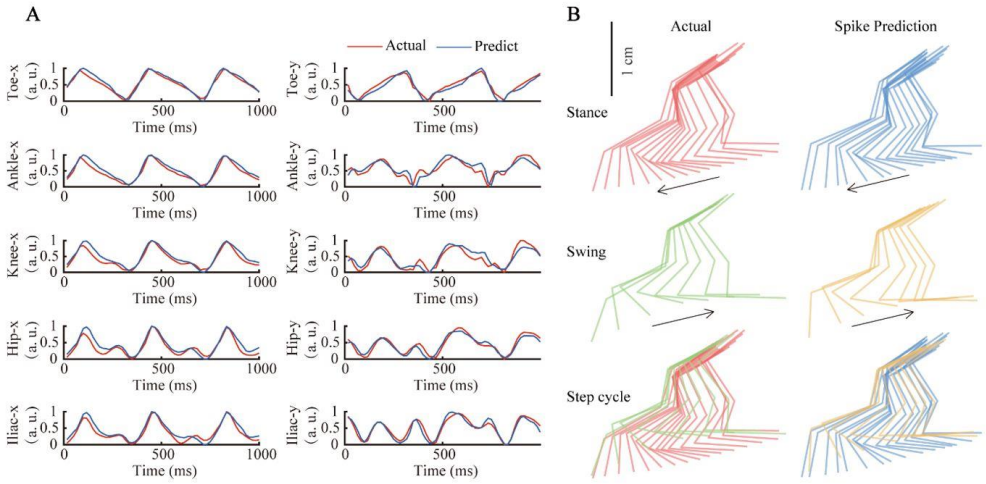


Figure 1. **LSTM decoding result.** A. Decoding of hindlimb joint coordinates trace. B. Original and predicted hindlimb joint trajectories.

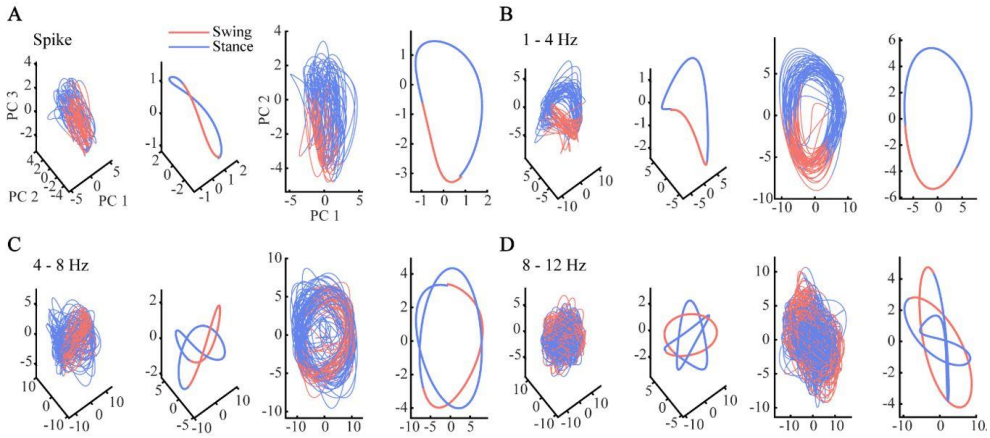


Figure 2. **The neural trajectory of intraspinal signals during movement.** A-D. Total and averaged 3D and 2D plots of spike, 1-4 Hz, 4-8 Hz, and 8-12 Hz LFP. Red and blue lines indicate the swing and stance phases of the step cycle, respectively.

**Disclosures:** **X. Li:** None. **P. Wang:** None. **J. Fan:** None. **X. Li:** None.

**Poster**

**PSTR056. Electrophysiology Techniques: Methods for Multicellular Recording In Vitro and In Vivo**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR056.10/VV43

**Topic:** I.04. Physiological Methods

**Support:** E12HN45921
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2021SHZDZX
21PJ1414400
LG202105-01
32200917

**Title:** A hyperflexible electrode array for long-term recording and decoding of intraspinal neuronal activity

**Authors: *J. FAN**, X. LI, P. WANG, F. YANG, B. ZHAO, J. YANG, Z. ZHAO, X. LI;
Ctr. for Excellence in Brain Sci. and Intelligence Technol., Shanghai, China

**Abstract:** Neural interfaces for stable access to the spinal cord (SC) electrical activity can benefit patients with motor dysfunctions. Invasive high-density electrodes can directly extract signals from SC neuronal populations that could be used for the facilitation, adjustment, and reconstruction of motor actions. However, developing neural interfaces that can achieve high channel counts and long-term intraspinal recording remains technically challenging. Here, we demonstrated a biocompatible SC hyperflexible electrode array (SHEA) with an ultrathin structure conducted by advanced nanofabrication technologies that minimizes mechanical mismatch between the interface and SC tissue and performed signal recording for more than two months in C57BL/6J mice (n = 5). To investigate SHEA's biocompatibility, we examined the density and morphology of astrocytes, microglia, and neuron on the cross-section of the sliced SC tissue near the implantation site (n = 3). We have also carried out gait test (n = 5) to further quantify the influence induced by the SHEA implantation on the behavioral level. Moreover, we decoded the neural signal in the spinal cord to predict the hind limb joint movement during a wheel running task (n = 2). Neural signal recording results showed that SHEA maintained stable impedance, signal-to-noise ratio, single-unit yield, and spike amplitude more than 2 months after implantation into C57BL/6J mouse SC. Gait analysis and SC tissue histology showed that SHEA implantation itself induced negligible behavioral effects and tissue Inflammation. In addition, the predicted position of 4 feet from spinal signals decoding largely reflected the real situation. SHEA offered a biofriendly neural interface for high-resolution, chronic signal recording in the spinal cord ventral horn. Thus, SHEA could offer an efficient and reliable SC neural interface for monitoring and potentially modulating SC neuronal activity associated with motor dysfunctions.

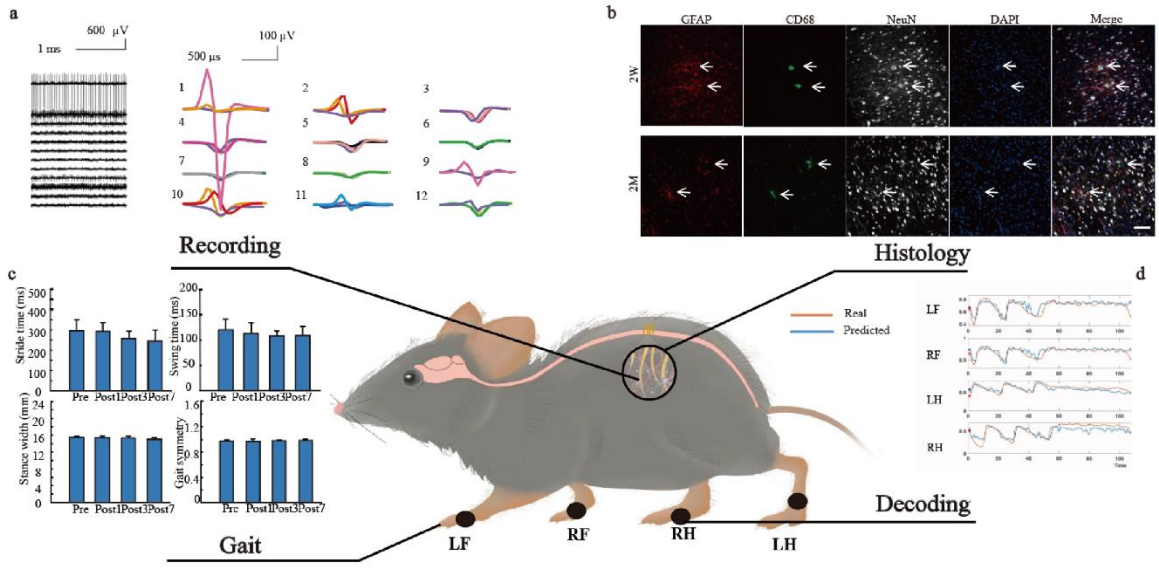



Figure 1. a, Typical raw data and sorted units from 12 electrode sites. b, Representative images of chronic tissue responses to SHEA at 2W and 2M after implantation. Scale bar, 100μm. c, The change of stance width, stride time, swing time, and gait symmetry before implantation post-implantation. d, Scatter plot of the decoded and actual coordinate of 4 feet.

**Disclosures:** **J. Fan:** None. **X. Li:** None. **P. Wang:** None. **F. Yang:** None. **B. Zhao:** None. **J. Yang:** None. **Z. Zhao:** None. **X. Li:** None.

**Poster**

**PSTR056. Electrophysiology Techniques: Methods for Multicellular Recording In Vitro and In Vivo**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR056.11/VV44

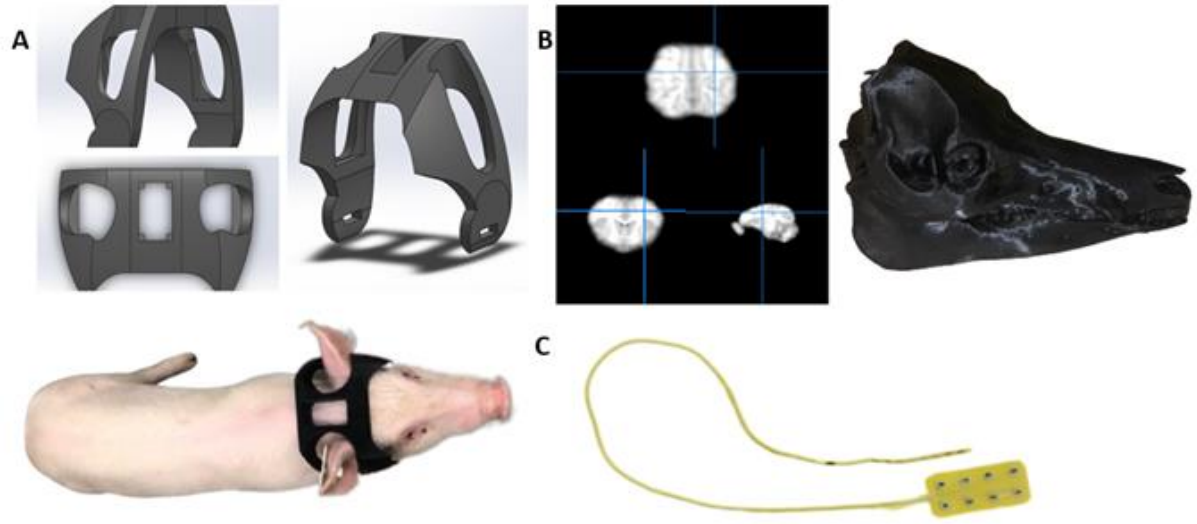
**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Title:** Stereotaxic development for a battery-less and wireless multichannel neuronal recorder

**Authors: *D. PARRADO**;
Florida Intl. Univ., Miami, FL

**Abstract: Stereotaxic development for a battery-less and wireless multichannel neuronal recorder**Authors: Daniel Parrado-Triana, Melany Gutierrez, John Volakis, and Jorge Riera Our team developed WiNS, a passive wireless neurosensing system [1] to replace implantable devices. It mitigatesheat radiation, tissue damage, and interference with neural readings. Transitioning from rats to pigs is essential forclinical trials. The device implanted in pigs will be similar to future human studies. A stereotaxic fixation helmetfor RF alignment is needed.We created an adjustable 3D printed helmet (Fig.1A) based on MRI of domesticated pigs (Fig.1B). SolidWorksdesigned it with holes for belts, straps, ears, and the WiNS interrogator. It was 3D printed with TPU 95A.Experiments were conducted on two pigs under anesthesia. Pig

physiology was monitored using the PowerLabdevice and LabChart. FDA-approved electrodes (Fig.1C) were placed in the somatosensory cortex. Stimulationblocks were recorded.We designed an adjustable helmet (Fig.1A) based on the pig's brain atlas and 3D SolidWorks. Functionality wasdemonstrated.**Figure 1.** A: In-Skull somatosensory fixation helmet and Pig wearing 3D printed helmet. B: Located somatosensorycortex at MRI pig's brain atlas with 3D printed swine skull C: FDA approved 4 channel stereo and strip electrodes(AD-TECH).[1] C. Moncion, et al. "Fully-Passive Wireless Implant for Neuropotential Acquisition: An In Vivo Validation,"IEEE J. Electromagn., RF Microwaves Med. Biol., vol. 3, no. 3, pp. 199-205, Sept. 2019, doi:10.1109/JERM.2019.2895657.[2] Fil, Joanne, et al. "High-resolution magnetic resonance imaging-based atlases for the young and adolescentdomesticated pig (Sus scrofa)." Journal of Neuroscience Methods, vol. 354, 2021, article no. 109107, ISSN 0165-0270, https://doi.org/10.1016/j.jneumeth.2021.109107.[3] Saikali, et al. A three-dimensional digital segmented and deformable brain atlas of the domestic pig. J NeurosciMethods. 2010 Sep 30;192(1):102-9. doi: 10.1016/j.jneumeth.2010.07.041. Epub 2010 Aug 6. PMID: 20692291.




**Disclosures: D. Parrado:** None.

**Poster**

**PSTR056. Electrophysiology Techniques: Methods for Multicellular Recording In Vitro and In Vivo**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR056.12/VV45

**Topic:** I.04. Physiological Methods

**Support:** KAKENHI Grant 17H03250, 26709024, 20H00244, 15H05917, 20H00614
NEDO

JST A-STEP
Nagai Foundation for Science & Technology
Takeda Science Foundation
TUT-DC Fellowship

**Title:** A 5-μm-diameter microneedle electrode-based chronic neural recording for freely moving mice

**Authors: *H. SASAKI**[1], K. YAMASHITA[2], S. SHIMIZU[1], R. NUMANO[2], K. KOIDA[2], T. KAWANO[2];
[1]Dept. of Electrical and Electronic Information Engin., [2]Inst. for Res. on Next-generation Semiconductor and Sensing Sci. (IRES2), Toyohashi Univ. of Technol., Toyohashi Aichi, Japan

**Abstract:** Quantitative observation of the physiological state of animals in freely moving is required in the neuroscience research, studying neurological diseases, and drug discovery. However, the conventional behavioral analysis-based ways do not sufficiently meet the requirements. *In vivo* electrophysiology with microelectrodes implanted in the brain is a preferred method for obtaining the quantitative observations. Although conventional microelectrodes provide high spatiotemporal resolution recordings of neuronal activities, these invasive electrodes cause tissue damage, limiting in the long-term recording capabilities. To address this issue, we propose a silicon-growth technology-based microelectrode with the diameter of < 5 μm. However, the microelectrode having high impedance characteristics and noise associated with the animal movement degrade the signal to noise ratios in the recording of freely moving animals. The goal of this study is to develop a technique for chronic neural recording using the microscale-needle electrode. We evaluated the long-term recording capabilities using the 5-μm-diameter silicon-microneedle electrode, comparing it with a commercially available tungsten-wire electrode (>10 μm in diameter). Both electrodes were implanted into individual mice. After 6 months, the tungsten electrode failed the number of electrodes detecting spikes in Peristimulus Time Histogram (PSTH) analysis, while the silicon-microneedle detected spike signals with three of four electrodes. This result suggested the superiority of the silicon-needle electrode for the long-term recording. We reduced noise including electromyograms (EMG) associated with mouse movement at spike frequency band. To minimize EMGs, we employed the reference electrode surrounding the base of silicon-needle electrode site and placed it on the tissue surface. In the recording from the primary visual cortex (V1) of the freely moving mouse, we detected spike signals responding to the visual stimulation, while power spectral density showed a reduction in noise across the spike frequency band. In conclusion, these findings in neural recording offer low-invasive chronic recording for freely moving animals using 5-μm-diameter microelectrode.

**Disclosures: H. Sasaki:** None. **K. Yamashita:** None. **S. Shimizu:** None. **R. Numano:** None. **K. Koida:** None. **T. Kawano:** None.

**Poster**

**PSTR056. Electrophysiology Techniques: Methods for Multicellular Recording In Vitro and In Vivo**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR056.13/VV46

**Topic:** I.04. Physiological Methods

**Support:** Science Research Center (SRC) for Novel Epitaxial Quantum Architectures (NRF-2021R1A5A1032996)
Basic Science Research Program through the National Research Foundation of Korea (NRF) (2020R1A2C2007285)
Institute of Applied Physics at Seoul National University

**Title:** Vertical ZnO nanotube electrode arrays grown on graphene for neuronal recording and imaging

**Authors: *J. LEE**[1], H. PARK[2], G.-C. YI[1];
[1]Seoul Natl. Univ., Seoul, Korea, Republic of; [2]Univ. of Minnesota, Univ. of Minnesota, Twin Cities, Minneapolis, MN

**Abstract:** Vertically ordered arrays of one-dimensional (1-D) nanostructures, such as nanowires, nanopillars, and nanotubes, are considered ideal functional components applicable for nanoscale neural probes. While progress has been made in incorporating top-down processed Si-based 1-D nanostructures into neural probe devices, their non-transparent nature limits the adaptation of essential optical imaging techniques for studying cell-nanostructure interfaces and cellular dynamics. In this study, we present the fabrication of vertical ZnO nanotube-based microelectrode arrays on graphene layers. By precisely controlling the position and dimensions of these vertically ordered ZnO nanotube structures on graphene, we establish individual interfaces with neurons. The vertical structure of ZnO nanotubes, characterized by a high aspect ratio, offers significant advantages for penetrating neuron cell membranes and capturing intracellular signals. For the fabrication of multichannel electrode arrays, ZnO nanotube arrays containing ultrathin nanowalls were grown on transparent multigraphene layers and coated with Ti/Au metal bilayers. Electrophysiological recordings using these vertical ZnO nanotube arrays on mouse and rat primary neurons reveal distinct intracellular- and extracellular-like potential activities. Notably, we measured positively depolarized signal amplitudes of 2 - 4 mV from cultured rodent hippocampal neurons on the arrays for 7 to 14 days in vitro (DIV). Similarly, we measured 0.1 - 0.2 mV negatively depolarized signals resembling extracellular-like spiking behavior. Additionally, we exploit the transparent characteristics of graphene and its catalyst-free growth capabilities to enable optical imaging. Confocal microscopy experiments demonstrate that transparent ZnO nanotube electrode arrays on graphene layers enable the imaging of hippocampal neurons with minimal light-induced artifacts. This graphene-based device is promising for investigating dynamic neuronal activity by simultaneously recording and imaging in vitro cell cultures. The vertical arrangement of ZnO nanotubes on graphene provides a powerful platform for advancing our understanding of neural dynamics and the cell-nanostructure interface.

**Disclosures: J. Lee:** None. **H. Park:** None. **G. Yi:** None.

**Poster**

**PSTR057. Neuromodulation Techniques: Electrical, Magnetic, Thermal, Optical, and Optogenetics**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR057.01/VV47

**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** NIH/NINDS (1U24NS113647)
USC Neurorestoration Center

**Title:** Subthreshold repetitive transcranial magnetic stimulation alters learning and memory performance of rats in the Barnes maze task

**Authors: *W. JIANG**[1], Z. LU[1], Z. JIN[1], Z. LI[1], Z. ZHU[1], Y. WANG[1], C. HSU[1], C. Y. LIU[1,2], D. SONG[1];
[1]Biomed. Engin., USC, Los Angeles, CA; [2]Neurolog. Surgery, USC Keck Sch. of Med., Los Angeles, CA

**Abstract:** Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neuromodulation technique widely used in clinical and experimental settings. Our recent studies have shown that even at low intensities, rTMS can alter the amplitude of evoked potentials and the firing rate of single-unit activities in anesthetized rats. In this study, to investigate the effects of rTMS on spatial learning and memory in behaving animals, we applied subthreshold rTMS to rats performing a Barnes maze (BM) task. The task consisted of 5 phases including a habituation phase to acclimate the animals to the restraint and environment, an acquisition phase where learning took place, an acquisition probe trial to assess spatial memory retrieval, a reversal learning phase to test cognitive flexibility, and a final reversal learning probe trial to evaluate adaptability of the learned responses. Twelve male Sprague Dawley rats were randomly divided into rTMS (n=6) and sham groups (n=6). During the acquisition and reversal learning phases, two sessions of 5-minute, 10 Hz rTMS or sham stimulation were applied above the medial prefrontal cortex (mPFC) of restrained rats for 10 consecutive days. Each stimulation session was immediately followed by a BM trial with an intertrial interval of ~15 minutes per day. No stimulation was applied during the habituation phase or probe trials. Results showed that the rTMS group required a longer time and made more errors in acquiring the task during the acquisition phase compared to the sham group. However, this trend was inversed during the reversal learning phase, when the rTMS group outperformed the sham group. Moreover, the rTMS group spent significantly more time (acquisition probe: 21±2 s; reversal learning probe: 21±3 s) in the area where the escape box was previously placed compared to the sham group (acquisition probe: 13±2 s; reversal learning probe: 14±2 s) in both probe trials (unpaired *t-test*, $p<0.05$). These findings indicate that while rTMS initially hinders spatial learning, it strengthens memories of previous target locations and enhances cognitive flexibility. These initial results hint at the potential clinical applicability of rTMS in addressing cognitive deficits associated with various neurological and neuropsychiatric disorders, such as obsessive-compulsive disorder (OCD) and autism spectrum disorder (ASD).

**Disclosures:** **W. Jiang:** None. **Z. Lu:** None. **Z. Jin:** None. **Z. Li:** None. **Z. Zhu:** None. **Y. Wang:** None. **C. Hsu:** None. **C.Y. Liu:** None. **D. Song:** None.

**Poster**

**PSTR057. Neuromodulation Techniques: Electrical, Magnetic, Thermal, Optical, and Optogenetics**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR057.02/VV48

**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** Murata Science Foundation Grant
Suzuken Memorial Foundation Grant
Grant from Nakatani Foundation for Advancement of Measuring Technologies in Biomedical Engineering
Grant-in-Aid for Exploratory Research (grant number 21K19755)
Grant-in-Aid for Scientific Research (B) (grant number 23H03416)

**Title:** Bidirectional modulation effects on neural activity induced by near-infrared light stimulation to the mouse inferior colliculus in vivo

**Authors: *T. TATENO**, F. SUGIMOTO, H. SATO;
Hokkaido Univ., Sapporo, Japan

**Abstract:** As neuromodulation and its clinical application, infrared neural stimulation (INS) is a promising area of interest among neural stimulation techniques, because of low-invasively modulating the activity of neural tissue mainly through small temperature changes. Additionally, INS has a possibility to provide a localized stimulation of the brain with less tissue damages. To apply INS, the inferior colliculus (IC) is one of the potential targets to treat auditory diseases and to develop artificial hearing devices because of the crucial auditory relay nuclei where auditory pathways converge during sound processing. Here, using continuous INS for a short period (10 to 30 s), we aimed to demonstrate the intensity-dependent bidirectional modulation of neural activity in the mouse IC in the presence and absence of sound. We also explored the stimulation parameters of INS to effectively modulate neural activity in a facilitatory or inhibitory manner. A mathematical model of INS-driven brain tissue was first simulated on a parallel computer, temperature distributions were numerically calculated, and stimulus parameters were selected from the simulation result. Subsequently, INS was actually administered to the IC of anesthetized mice, and the modulation effect on neural activity was measured using an electrophysiological method. We found that the modulation effect of INS on spontaneous neural activity was bidirectional between facilitatory and inhibitory effects. Furthermore, the modulation effects were dependent on the stimulus intensities and the layer depth from the IC surface. Additionally, the modulation effect on the sound-evoked response produced only an inhibitory effect at all examined stimulus intensities. Histological analysis of INS-stimulated IC tissue provided damage threshold estimation, and no/little damage was observed in a range of

our stimulation intensities. Thus, this study provides an important physiological evidence on the response properties of IC neurons to INS. We hope that the INS will be applied to the development of new therapies for neurological diseases and functionally supporting devices for the auditory central processing.

**Disclosures:** **T. Tateno:** None. **F. Sugimoto:** None. **H. Sato:** None.

**Poster**

**PSTR057. Neuromodulation Techniques: Electrical, Magnetic, Thermal, Optical, and Optogenetics**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR057.03/VV49

**Topic:** I.08. Methods to Modulate Neural Activity

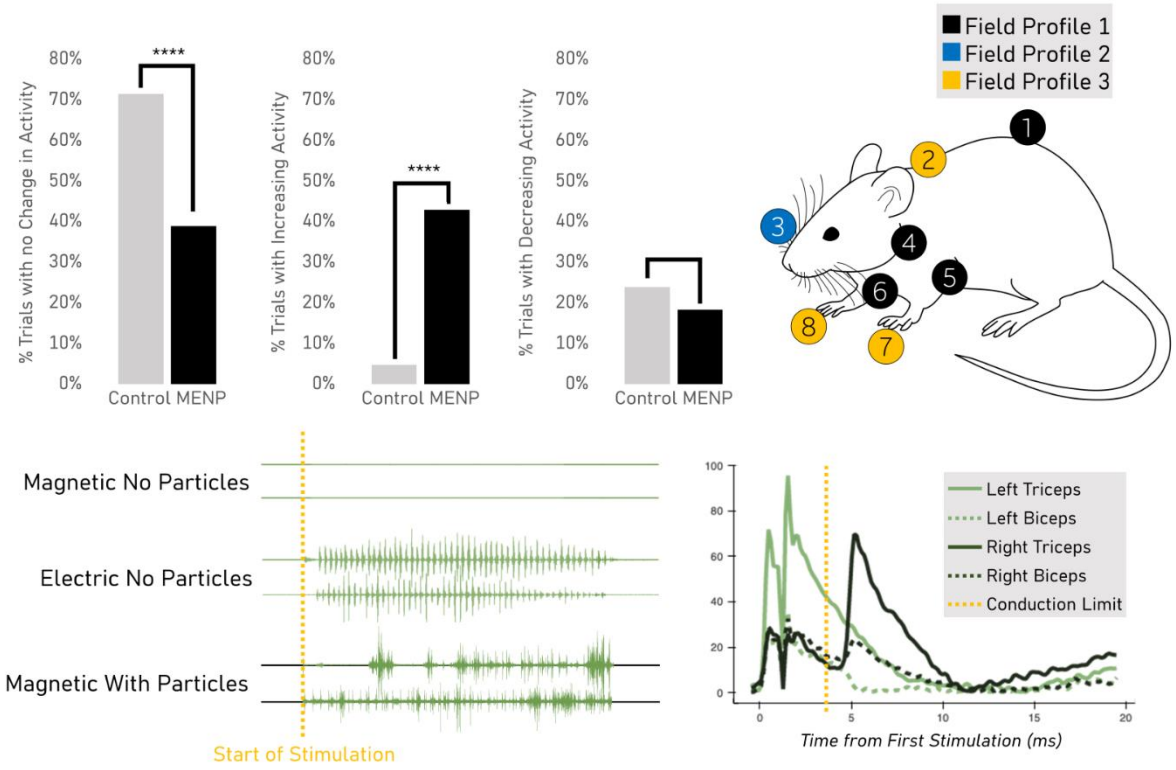
**Support:** DARPA Contract N6600119C4019
NSF Grant ECCS-1935841

**Title:** Wireless multi-channel motor cortex stimulation with magnetoelectric neural interfaces

**Authors: *E. ZHANG**[1], M. ABDEL-MOTTALEB[2], M. CAMPOS[3], B. NAVARRETE[5], Y. YILDIRIM[3], V. ANDRE[4], M. SHOTBOLT[3], I. SMITH[3], P. LIANG[6], B. R. NOGA[7], S. KHIZROEV[3];
[1]Electrical and Computer Engin., [2]Biomed. Engin., Univ. of Miami, Coral Gables, FL; [4]Engin., [3]Univ. of Miami, Miami, FL; [5]Florida Intl. Univ., Miami, FL; [6]Cell. Nanomed, Irvine, CA; [7]Miami Project, Univ. of Miami Miller Sch. of Med., Miami, FL

**Abstract:** The living brain with its 100 billion neurons and 100 trillion connections is incredibly difficult to study while intact. Despite this, localized brain stimulation is clinically relevant in restoring sensory and motor functions and in treating neurological diseases such as Parkinson's and essential tremor. However, the risks associated with implanting electrodes in brain tissue (e.g., surgical complications, inflammation, and degrading performance) confine the technique to niche, last resort medical cases and prohibits exploring functional and enhancement applications. In the effort to find alternatives to electrodes, magnetic fields have emerged alongside ultrasound, guided electric fields, and optogenetics as one of the leading paths forward. However, modern magnetic methods such as magnetomechanical and Transcranial Magnetic stimulation have tradeoffs with temporal and spatial resolution, especially for deep brain regions. Recently proposed Magnetoelectric Nanoparticles (MENPs) can offer the best of both worlds, obtaining both high spatial localization and low latency activation. The particles work as nano-scale transducers, efficiently converting external, low-power magnetic fields into short range, stimulating electric fields. This approach is blood brain barrier permeable, reducing the need for extensive surgery, and can be guided into place by magnetic fields and antibodies. Existing studies have successfully shown broad-scale activation of neural responses, sufficient to trigger neural activity *in vitro* and adjust behavioral responses *in vivo*. This study further enhances the

method by demonstrating precision control over 7 motor responses corresponding to a 1 $mm^2$ region of the brain. The response differentiation is controlled completely externally through varied magnetic spatio-temporal profiles, which opens the possibility for a non-surgical, wireless, multichannel brain-machine interface.




**Disclosures:** **E. Zhang:** None. **M. Abdel-Mottaleb:** None. **M. Campos:** None. **B. Navarrete:** None. **Y. Yildirim:** None. **V. Andre:** None. **M. Shotbolt:** None. **I. Smith:** None. **P. Liang:** None. **B.R. Noga:** None. **S. Khizroev:** None.

**Poster**

**PSTR057. Neuromodulation Techniques: Electrical, Magnetic, Thermal, Optical, and Optogenetics**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR057.04/VV50

**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** Pioneer Award
NIH BRAIN Initiative and the National Institute for Neurological Disorders and Stroke
McGovern Institute for Brain Research at MIT
K. Lisa Yang and Hock E. Tan Center for Molecular Therapeutics at MIT

**Title:** Wireless Modulation of Membrane Potential and Behavior with Magnetoelectric Nanodiscs

**Authors: *Y. KIM**, N. DRISCOLL, M. MANTHEY, N. KENT, F. KOEHLER, E. PANIAGUA, P. ANIKEEVA;
MIT, Cambridge, MA

**Abstract:** Nanoparticle-mediated transduction of physiologically benign weak magnetic fields into bio-readable electrical signals offers a minimally-invasive alternative to implantable electric neural modulation tools. Although effective at the macro- and microscale, magnetoelectric neuromodulation at the nanoscale - the scale of individual cells and receptors remains elusive. Here we synthesize nanoparticles with a record magnetoelectric transduction efficiency. In these core-double shell nanodiscs, magnetostriction (magnetic field to strain) is enhanced by depositing a thin layer of cobalt ferrite onto a magnetite nanodisc. The electric field is then generated in a layer of piezoelectric barium titanate. Magnetoelectric nanodiscs (MENDs) with a surface density of 1 mg/mm$^2$ on primary hippocampal neurons evoke robust calcium ion concentration transients in response to magnetic field stimuli. Given that individual MENDs can only generate ~30 μV in the applied magnetic field, which is far below the firing threshold for a typical neuron, we investigated the possible mechanism underlying our observations. We propose a biophysical model that combines two insights: (1) the steady-state solution of 3-dimensional cable theory for multiple microelectrode stimulation and (2) a stochastic model of the repetitive subthreshold neuronal excitation. By combining the insights of our model with the in-vitro optimization of the magnetic field conditions and particle concentrations, we identify stimulation parameters suitable for implementation in vivo. We then demonstrate the ability of the MENDs to trigger activity in neurons in the ventral tegmental area (VTA) in mice as recorded photometrically and through quantification of the immediate early gene c-fos. We also show magnetic control of place preference in untethred genetically-intact mice following 1.5 μL injections of MENDs into the VTA at concentrations of 1 mg/mL, which is ~100 times lower than that necessary for any prior magnetic neuromodulation approach reliant on nanomaterials. The demonstration of MEND-mediated neuromodulation in vitro and in vivo and the proposed biophysical mechanism underlying our observations suggests further directions for optimization of wireless magnetoelectric neuromodulation for neuroscience research.

**Disclosures: Y. Kim:** None. **N. Driscoll:** None. **M. Manthey:** None. **N. Kent:** None. **F. Koehler:** None. **E. Paniagua:** None. **P. Anikeeva:** None.

**Poster**

**PSTR057. Neuromodulation Techniques: Electrical, Magnetic, Thermal, Optical, and Optogenetics**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR057.05/VV51

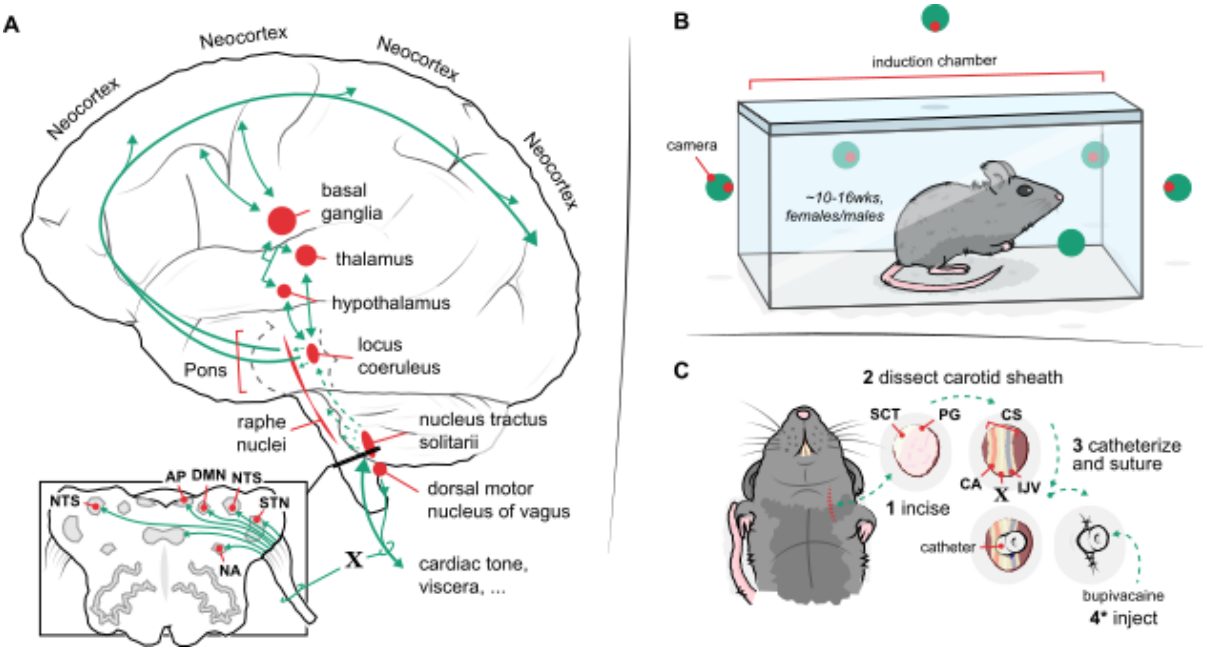
**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** Lundbeckfonden - DANDRITE-R248-2016-2518; R344-2020-300; R351-2020-1095;
Novo Nordisk Foundation - NNF20OC0064395
European Research Council Starting - 638730

**Title:** Potentiation of general anesthesia by local blockade of the peripheral vagus nerve

**Authors: *S. ARVIN**[1], A. N. GLUD[2], K. YONEHARA[3];
[1]Dept. of Neurosurgery, Aarhus Univ. Hosp., Aarhus, Denmark; [2]Dept. of Neurosurg., Aarhus Univ. Hosp., Aarhus, Denmark; [3]DANDRITE- Danish Res. Inst. of Translation, DANDRITE-Danish Res. Inst. of Translation, Aarhus C, Denmark

**Abstract:** Background: General anesthetics are used extensively in modern medicine, but the associated cardiopulmonary risks and chronic neural effects pose a growing issue to aging patient populations. Anesthetic premedication presents a promising method to reduce the risks associated with high-dose general anesthesia. Methods: The present study was designed to probe the anesthetic sparing properties of acute vagus nerve blockade in mice. To this end, we treated the vagus nerve with either bupivacaine or saline (control) via a pre-installed neck catheter one hour prior to isoflurane gas anesthesia. We assessed the anesthetic potency by computing the anesthetic induction time using a deep learning-based method for pose estimation. Results: When preceded by vagus nerve blockade, the induction time of isoflurane gas anesthesia decreased by 22% (-15 seconds, $P < 0.05$), consistent with anesthetic potentiation. In addition, vagus nerve blockade exhibited hemodynamic stabilizing effects. Potential confounders, such as age, had minor significance. Conclusion: Vagus nerve blockade may be an effective general anesthetic adjuvant with hemodynamic stabilizing effects. Further research is needed to confirm the findings presented in this preliminary study, e.g., using targeted vagus nerve blockade and extensive hemodynamic monitoring.




**Disclosures:** **S. Arvin:** None. **A.N. Glud:** None. **K. Yonehara:** None.

**Poster**

**PSTR057. Neuromodulation Techniques: Electrical, Magnetic, Thermal, Optical, and Optogenetics**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR057.06/VV52

**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** DEEPER (ICT-36-2020-101016787)
Human Brain Project SG3 (945539)
CERCA Programme (2017-SGR-1442 and 2017-SGR-00465)
DEEP RED Grant (PID2019-111493RB-I00)
la Caixa foundations (ID 100010434)
Predoctoral fellowship FPI (reference BES-2017-082496)

**Title:** Three-photon infrared stimulation of endogenous neuroreceptors in vivo

**Authors: *R. SORTINO**[1], M. CUNQUERO[2], G. CASTRO-OLVERA[2], R. GELABERT[3], M. MORENO[3], F. RIEFOLO[1], C. MATERA[1], N. FERNÀNDEZ-CASTILLO[4], J. M. LLUCH[3], J. HERNANDO[3], P. LOZA-ALVAREZ[2], P. GOROSTIZA[1];
[1]Inst. for Bioengineering of Catalonia, Barcelona, Spain; [2]Inst. de Ciències Fotòniques, Castelldefels, Spain; [3]Univ. Autònoma de Barcelona, Bellaterra, Spain; [4]Univ. de Barcelona, Barcelona, Spain

**Abstract:** To interrogate neural circuits and crack their codes, it is essential to combine *in vivo* brain activity imaging and spatiotemporally precise stimulation in three dimensions using genetic or pharmacological specificity. This challenge requires the deep penetration and focusing that can only be provided by infrared light and multiphoton excitation, which has led to a surge in methods for two-photon optogenetics and photopharmacology in recent years. However, three-photon brain stimulation *in vivo* remains to be demonstrated. Here, we report the regulation of neuronal activity in zebrafish larvae by three-photon excitation of a photoswitchable muscarinic agonist at 50 pM, a billion-fold lower concentration than used for uncaging, and with mid-infrared light of 1560 nm, the longest photostimulation wavelength reported so far. Photoresponses are robust, physiologically relevant, and offer an unprecedented way to modulate brain activity in wild-type animals with spatiotemporal resolution and pharmacological specificity. We also compute the multiphoton absorption probabilities and cross-sections of photoswitchable molecules, predicting that azobenzene-based ligands designed for one-photon excitation with ultraviolet and visible light have high three-photon absorption cross-section and can be used directly with pulsed infrared light. The wide application of three-photon pharmacology will deeply impact basic neurobiology and the progression of neuromodulation therapies based on light.

**Disclosures:** **R. Sortino:** None. **M. Cunquero:** None. **G. Castro-Olvera:** None. **R. Gelabert:** None. **M. Moreno:** None. **F. Riefolo:** None. **C. Matera:** None. **N. Fernàndez-Castillo:** None. **J.M. Lluch:** None. **J. Hernando:** None. **P. Loza-Alvarez:** None. **P. Gorostiza:** None.

**Poster**

**PSTR057. Neuromodulation Techniques: Electrical, Magnetic, Thermal, Optical, and Optogenetics**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR057.07/VV53

**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** Lundbeck Fonden Experiment Grant R346-2020-1822
Innovation Fund Denmark Grant 9068-00025A

**Title:** Immediate transcranial evoked potential of the primary motor hand area

**Authors: *L. TOMASEVIC**[1], M. M. BECK[1], L. CHRISTIANSEN[1], M. MADSEN[1], A. F. JADIDI[1], M. C. VINDING[1], T. O. BERGMANN[2,3], A. THIELSCHER[1,4], H. R. SIEBNER[1,5,6]; [1]DRCMR, MR-forskning, Afs. 714, Copenhagen Univ. Hosp. Amager and Hvidovre, Hvidovre, Denmark; [2]Neuroimaging Ctr. (NIC), Johannes Gutenberg Univ. Med. Ctr. Mainz, Johannes Gutenberg Univ., Mainz, Germany; [3]Leibniz Inst. for Resilience Res., Mainz, Germany; [4]Dept. of Hlth. Technol., Tech. Univ. of Denmark, Kgs Lyngby, Denmark; [5]Dept. of Neurol., Copenhagen Univ. Hosp. Bispebjerg and Frederiksberg, Copenhagen, Denmark; [6]Dept. of Clin. Medicine, Fac. of Hlth. and Med. Sci., Univ. of Copenhagen, Copenhagen, Denmark

**Abstract: Background:**
Transcranial magnetic stimulation (TMS) combined with electroencephalography (EEG) is widely used to investigate excitability and connectivity of the stimulated cortical region by measuring the transcranially evoked potentials (TEPs). So far, they have been mainly used to study the late (>30 ms) cortical responses, due to the artifacts induced by the TMS. In fact, the first 5 ms are covered by the magnetically induced ringing artifact, and the first 10 to 20 ms are affected by the twitch of the scalp muscles. In this study, we set out to unveil the immediate TEPs (iTEPs) of the primary motor hand area (M1-HAND) by minimizing these artifacts.
**Methods:**
We recorded iTEPs of M1-HAND in 14 healthy volunteers in whom TMS did not evoke any muscular twitches in the scalp. Moreover, we recorded EEG at high sampling rates (50 kHz) and 10.3 kHz anti-aliasing filter to shorten the TMS pulse artifact to less than 2 ms. We characterized the properties of iTEPs by varying stimulation intensities, current directions, and target sites.
**Results:**
We observed a positive deflection superimposed by a series of peaks with ~1.2-1.4 ms inter-peak interval in electrodes close to the M1-HAND stimulation site. The amplitude of iTEPs scaled positively with TMS intensity, and they changed quantitatively and qualitatively with the current direction. Importantly, they were site specific, as they disappeared when we stimulated over the

midline or over the parietal cortex.
**Discussion:**
Here, we show that single-pulse TMS of M1-HAND evokes a fast EEG response within a few milliseconds after the pulse. This immediate TEP cannot be accounted for by known artifacts and may reflect direct neural excitation of the M1-HAND after TMS.

**Disclosures: L. Tomasevic:** None. **M.M. Beck:** None. **L. Christiansen:** None. **M. Madsen:** None. **A.F. Jadidi:** None. **M.C. Vinding:** None. **T.O. Bergmann:** None. **A. Thielscher:** None. **H.R. Siebner:** None.

**Poster**

**PSTR057. Neuromodulation Techniques: Electrical, Magnetic, Thermal, Optical, and Optogenetics**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR057.08/VV54

**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** Innovative Medicines Initiative 2

**Title:** Chemogenetic activation of parvalbumin+ interneurons in orbitofrontal cortex leads to increased cerebral blood volume and social dysregulation

**Authors: *E. KHATAMSAZ**[1,2], T. M. IONESCU[1], F. STOLLER[1], B. HENGERER[1];
[1]Boehringer Ingelheim Pharmaceuticals, Biberach an der Riß, Germany; [2]Ulm university, Ulm, Germany

**Abstract:** The Psychiatric Ratings using Intermediate Stratified Markers (PRISM) project focuses on understanding the biological background behind social deficits, especially social withdrawal, as a critical step in developing new treatments for psychiatric disorders. In PRISM1, reduced connectional integrity in fiber tracts such as Forceps minor has been indicated in low social individuals. These fiber tracts are involved in the Default Mode Network (DMN) and social network sharing a common region, the Orbitofrontal Cortex (OFC). This preclinical study, as a part of PRISM2, aims to back translate data from clinical studies by investigating the role of parvalbumin (PV+) interneurons in OFC, which are associated with social deficits. The critical role of PV+ interneurons in Excitatory/Inhibitory balance underscores their potential as candidates for the identification of novel treatments for psychiatric disorders.We studied the effect of OFC hypoactivation on social behaviors in mice by using Radiofrequency identification (RFID)-assisted SocialScan video tracking software. To induce hypoactivation, we introduced an excitatory DREADD (designer receptors exclusively activated by designer drugs) to PV+ interneurons using a PV-Cre mouse line. Mice were injected with either AAV-hSyn-DIO-hM3D(Gq)-mCherry virus (n=12) or AAV-hSyn-DIO-mCherry (n=12) as control virus. hM3Dq receptors were acutely activated with Clozapine-N-oxide (CNO). Additionally, as part of the ongoing experiment, we are conducting functional ultrasound (fUS) imaging in an oblique plane

to observe the effect of this manipulation on the connectivity between OFC and other regions of DMN in both hM3Dq (n=10) and control (n=10) group, as well as the changes in cerebral blood volume (CBV) changes. The administration of CNO induced social dysregulation in DREAAD mice, as demonstrated by various social parameters (approach, fight, etc.). In situ hybridization using a neuronal activity marker indicated higher activation of PV+ interneurons in the hM3Dq group. In conclusion, we hypothesize that the activation of PV+ interneurons in the OFC leads to altered connectivity in the DMN, accompanied by social dysfunction in mice, supporting the clinical findings of the PRISM project.

**Disclosures: E. Khatamsaz:** None. **T.M. Ionescu:** None. **F. Stoller:** None. **B. Hengerer:** None.

**Poster**

**PSTR057. Neuromodulation Techniques: Electrical, Magnetic, Thermal, Optical, and Optogenetics**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR057.09/VV55

**Topic:** I.04. Physiological Methods

**Support:** NSF 1545858

**Title:** Thermalflex: A Flexible Microfluidic-Based Cooling Module for Focal Brain Temperature Control and Neural Activity Modulation

**Authors: *Y. TIAN**[1], J. R. LOPEZ RUIZ[2], D. YAN[1], V. LANZIO[1], E. YOON[3];
[2]Electrical Engin. & Computer Sci., [1]Univ. of Michigan, Ann Arbor, Ann Arbor, MI; [3]EECS, Univ. of Michigan, Ann Arbor, Superior Township, MI

**Abstract:** Temperature plays a vital role in physiological processes, with meticulous control of brain temperature surfacing as a key determinant in modulating neural activity. However, existing Peltier-based cooling modules face difficulties such as uneven heat distribution that can cause freezing at the surface of the brain, inefficient brain temperature regulation at deeper brain region targets, and substantial brain damage due to their rigid and large structures. In response to these challenges, we introduce a flexible microfluidic channel-based temperature control probe (ThermalFlex), with cross-sectional dimensions of 150 µm x 45 µm, minimizing size to 90um x 45 um. The design combines advanced neural interface technology with an external cooling source to achieve superior cooling performance. The primary advancements designed to improve the suitability of rodent animal research involve a six-fold reduction in brain tissue damage by decreasing the size, a 46-fold reduction in the polyimide insulation tube count, and 20,000 times smaller Young's modulus (Petersen et al., 2021). Utilizing flexible materials PDMS and polyimide also enhances heat distribution, promoting a superior cooling effect at the cooling probe's tip. Our research demonstrates a temperature drop of 14 degrees Celsius in the hippocampus and a 10 degrees Celsius reduction in the nucleus accumbens of a Sprague Dawley

rat (n=4), using Thermalflex, maintained for an uninterrupted 30 minutes during an acute experiment setup. By combining this setup with a temperature sensor and a 64-channel flexible neural recording probe, we were able to gather electrophysiological data showing various effects of temperature fluctuations on local field potential shifts in the hippocampus. This significantly expands our understanding of thermal modulation in neural settings.

**Disclosures:** **Y. Tian:** None. **J.R. Lopez Ruiz:** None. **D. Yan:** None. **V. Lanzio:** None. **E. Yoon:** None.

**Poster**

**PSTR057. Neuromodulation Techniques: Electrical, Magnetic, Thermal, Optical, and Optogenetics**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR057.10/VV56

**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** RGPIN-2020-06930

**Title:** The effect of the h4MDi-chemogenetic virus on responses to sensory stimuli in rat area S1FL: implications for modulating neural circuits

**Authors: *T. DAVID**, A. BORTEL, A. SHMUEL;
McGill Univ. Integrated Program in Neurosci., Montreal, QC, Canada

**Abstract:** Chemogenetics has emerged as a powerful tool for manipulating neuronal activity and investigating the function of neural circuits. Here we aim to gain insight into the effects of a chemogenetic virus utilizing the h4MDi receptor on neuronal activity in the rat primary somatosensory cortex. To this end, Sprague-Dawley rats were injected with an Adeno-Associated Virus (AAV) containing the modified inhibitory receptor h4MDi expressed under the control by either the HSyn or CAMKII promoter. Optical imaging (OI) was employed to detect the cerebral blood volume responses in the S1FL region, providing precise guidance for the AAV injection locations. Following the virus incubation period, electrophysiological recordings were performed in conjunction with forepaw electrical stimulation. To activate the h4MDi receptor, we utilized the specific ligands C21 and DCZ. We investigated the influence of different promoters on the suppression of local neurons by the h4MDi receptor.Our experimental results revealed that the h4MDi-chemogenetic virus under the control of the CAMKII promoter suppressed the responses of pyramidal neurons in area S1FL. Forty-five minutes following the ligand injection, the CAMKII promoter significantly suppressed neuronal activity, resulting in an 85-90% reduction in local field potentials (LFP) and current source density (CSD), as well as a 65-75% decrease in multi-unit activity (MUA). However, 4 hours following ligand administration, there was a partial recovery of neuronal activity, with approximately 30-40% restoration in LFP and CSD, and 15-20% recovery in MUA. Interestingly, we found that the HSyn promoter affected local neurons in an unexpected manner. Instead of suppression, the

h4MDi receptor under the HSyn promoter increased neural activity. We observed increases of 50-60% in the LFP and CSD responses and 40-50% in MUA 60 minutes after the ligand administration. No complete return to baseline was observed throughout the duration of the experiment. The AAV virus containing HSyn or CAMKII promoters exhibited similar spreading infection patterns.These findings provide insight into the suppressive effects of h4MDi chemogenetic viruses on neuronal activity in rat S1FL. The selection of promoter influences neuronal response modulation. The potent suppressive effects of h4MDi - particularly when combined with the DCZ ligand and the CAMKII promoter - highlight their potential for effective modulation of local pyramidal neurons. The implications of these findings extend to the field of neural circuit modulation, where the capacity to control neuronal activity precisely holds promise for understanding sensory processing.

**Disclosures:** **T. David:** None. **A. Bortel:** None. **A. Shmuel:** None.

**Poster**

**PSTR057. Neuromodulation Techniques: Electrical, Magnetic, Thermal, Optical, and Optogenetics**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR057.11/VV57

**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** NIH R01 NS119395
NIH R01 NS116464-01
University of Washington Big Data for Genomics & Neuroscience Training Grant
University of Washington Mary Gates Scholarship
National Science Foundation Graduate Research Fellowships Program
Weill Neurohub
Washington National Primate Research Center P51 OD010425

**Title:** Optimized large-scale and chronic optogenetic cortical interface for non-human primates

**Authors: *D. GRIGGS**[1], J. BLOCH[2], S. FISHER[4], W. OJEMANN[5], K. COUBROUGH[3], K. KHATEEB[2], M. CHU[3], A. YAZDAN-SHAHMORAD[3];
[1]Univ. of California, Davis, Davis, CA; [2]Univ. of Washington, [3]Univ. of Washington, Seattle, WA; [4]Univ. of California San Diego, Univ. of California San Diego, San Diego, CA; [5]Univ. of Pennsylvania, Philadelphia, PA

**Abstract:** High spatial and temporal precision and cell type specificity make optogenetics a powerful tool for studying fundamental neural mechanisms and developing neurorehabilitation techniques. Here we demonstrate an optimized large-scale optogenetic cortical interface for chronic non-human primate experiments (NHPs) [1, 2]. This interface consists of a chamber housing a custom built multi-modal artificial dura (MMAD), which is an advancement in

comparison to artificial duras used for optical imaging in that platinum particles are printed into a biocompatible and transparent polymer enabling electrical stimulation and recording in combination with optical access to the cortex [3]. We have surgically implanted the MMAD in two rhesus macaques which provides both optical access to about 2.7 $cm^2$ and recording capability from about 1 $cm^2$ of the posterior parietal cortex (PPC). We also developed a custom LED array compatible with our MMAD for optical stimulation. To achieve large-scale optogenetic expression, we delivered AAV-hSyn-Jaws-GFP into PPC using convection enhanced delivery (CED), an efficient pressure-based viral delivery approach [2, 4-5]. This interface improves upon the stability and scale of our previous interface iterations [4]. We confirmed expression across large cortical areas (>2 $cm^2$) with both neurophysiology and epifluorescent imaging. Furthermore, using this interface we observed that optogenetic modulation of PPC leads to longer reaches in a center-out reach task. Our optimized design supports 3+ months of optical access before tissue growth blocks optical access, in comparison to 2-4 weeks in our previous version, and uses up to 16 LEDs for patterned optical stimulation, which is an order of magnitude improvement over our previous setup. Lastly, our custom designed MMAD enables our printed circuit boards to be clamped on the MMAD polymer only for the duration of stimulation and recording [3] making the entire setup more stable. Our animals (N=2) continue to participate in experiments 15 and 22 months after chamber implantation. This work [6] will set the stage for the development of stable, large-scale, multi-modal neural modulation protocols for the purpose of studying cortical organization and plasticity, and developing neurorehabilitation techniques. References: [1] DJ Griggs et al., *SPIE,* 2019 [2] DJ Griggs et al., *EMBC,* 2022 [3] DJ Griggs et al., *J. Neural Eng.,* 2021 [4] A Yazdan-Shahmorad et al., *Neuron,* 2016 [5] K Khateeb et al., *J. Vis. Exp.,* 2019 [6] DJ Griggs* and J Bloch* et al., *(in preparation)*

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**Poster**

**PSTR057. Neuromodulation Techniques: Electrical, Magnetic, Thermal, Optical, and Optogenetics**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR057.12/VV58

**Topic:** I.06. Computation, Modeling, and Simulation

**Support:** Abbott Neuromodulation
NIH OT2 OD025340
REVA contract #75N98022C000018
Case Western Reserve University SOURCE program

**Title:** Using micro-CT to quantify porcine spinal cord anatomical measurements with intact dura mater

**Authors: *J. CHIN**[1,3], D. LUST[1,3], A. UPADHYE[3,1], R. CONTRACTOR[1], A. SHUNMUGAVEL[1,3], M. SETTELL[4], M. BRUKER-HAHN[5], S. F. LEMPKA[5], K. LUDWIG[4], I. LAVROV[6], M. ZHANG[7], A. CROFTON[2], A. SHOFFSTALL[1,3];
[1]Dept. of Biomed. Engin., [2]Dept. of Anat., Case Western Reserve Univ., Cleveland, OH; [3]Advanced Platform Technol. Center, Rehabil. Res. and Develop., Louis Stokes Cleveland Dept. of Veteran Affairs Med. Ctr., Cleveland, OH; [4]Dept. of Biomed. Engin., Univ. of Wisconsin Madison, Madison, WI; [5]Dept. of Biomed. Engin., Univ. of Michigan, Ann Arbor, MI; [6]Dept. of Neurol. and Biomed. Engin., Mayo Clin., Rochester, MN; [7]Abbott Neuromodulation, Plano, TX

**Abstract:** Spinal cord stimulation (SCS) is an FDA-approved therapeutic modality to treat chronic, refractory, and intractable back pain. In the US, SCS has been applied to over 50,000 patients annually. Despite the significant rate of effective pain relief (60%), SCS is prone to side effects due to lead migration, off-target stimulation, etc., limiting its therapeutic potential. In addition, the mechanism of action of SCS has not yet been thoroughly revealed. Therefore, there exists substantial interest from the industry and the scientific community to better understand the mechanistic underpinnings of SCS. Animal models, in particular porcine models, are ideal for performing SCS research due to their spinal dimensions similar to humans. In addition, the neural response to electrical stimulation can be recorded with anesthetized pigs. The *in vivo* experimental data can then be analyzed using computational models to evaluate novel electrode design parameters and implantation positions. However, to accomplish this, there is a need to study the neuroanatomy of the pigs' spinal cord with intact dura to provide more information on the neural stimulation pathways and mechanisms of action. In our study, porcine spinal cords containing spinal levels T10 to L2 with intact dura were stained with osmium tetroxide and imaged using micro-CT (μCT). Samples included dorsal root ganglia and proximal segments of ventral and dorsal rami. The μCT scans were then stitched together to create a high-resolution 3D volume of the entire sample. The resulting volumes of porcine spinal cord demonstrated superior resolution to conventional spinal imaging modalities such as MRI or traditional CT. The findings show that the pig spinal cords closely resembled human spinal cords with respect to size and presence of dorsal root entry zone (DREZ), dorsal/ventral rootlets, and dorsal root ganglia. However, porcine spinal cords differ dramatically from human spinal cords with respect to rootlet counts and angles. Porcine cords contained more ventral rootlets (20-30) than dorsal rootlets (10-15) and have relatively large rostral and caudal rootlet angles (>150 °), resulting in narrowing of rootlet orientation distal from the DREZ. Additionally, we segmented the micro-CT images to generate 3D models of the spinal cord for better visualization of rootlets. Overall, our findings suggest that using μCT on *ex vivo* porcine spinal cord samples with intact dura can reveal detailed anatomical structures allowing for more accurate characterization of the spinal anatomy. Hence, we hope that this work will facilitate the interpretation of porcine SCS electrophysiology experiments and SCS computational modeling.

**Disclosures: J. Chin:** None. **D. Lust:** None. **A. Upadhye:** None. **R. Contractor:** None. **A. Shunmugavel:** None. **M. Settell:** None. **M. Bruker-Hahn:** None. **S.F. Lempka:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Abbott Neuromodulation, Medtronic plc, Neuromodulation Specialists LLC, Presidio Medical Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CereGate, Hologram Consultants LLC, Presidio Medical Inc. **K. Ludwig:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroOne

Medical Inc., NeuronOff Inc. F. Consulting Fees (e.g., advisory boards); Cala Health, Blackfynn, Abbott, Batelle, Galvani, Boston Scientific, NeuronOff Inc. **I. Lavrov:** None. **M. Zhang:** A. Employment/Salary (full or part-time); Abbott Neuromodulation. **A. Crofton:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Karamedica Inc. F. Consulting Fees (e.g., advisory boards); Karamedica Inc, ChitozanHealth LLC. **A. Shoffstall:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuronOff Inc. F. Consulting Fees (e.g., advisory boards); NeuronOff Inc.

**Poster**

**PSTR057. Neuromodulation Techniques: Electrical, Magnetic, Thermal, Optical, and Optogenetics**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR057.13/VV59

**Topic:** I.04. Physiological Methods

**Support:** NIH Grant R01NS116080

**Title:** Surface modifications of boron diamond microelectrodes for neurotransmitter detection with fast-scan cyclic voltammetry

**Authors: *J. R. SIEGENTHALER**[1,2], B. KEPROS[1], N. J. LORENZ[1,7], V. ÖRNBRATT[1], J. B. LANDGRAF[1], B. GUPTA[3], M. L. PERILLO[4], R. RECHENBERG[1], G. H. U. BANNA[5], D. GALSTYAN[1], A. HARDY[1], M. F. BECKER[1], E. K. PURCELL[2,3,4,6], W. LI[1,2,4,6];
[1]Ctr. Midwest: Coatings and Diamond Technologies Div., Fraunhofer USA, East Lansing, MI; [2]Electrical and Computer Engin., [3]Neurosci. program, [4]Biomed. Engin., Michigan State Univ., East Lansing, MI; [5]Michigan State Univ., Electrical and Computer Engineering, MI; [6]Inst. for Quantitative Hlth. Sci. and Engin., Michigan State Univ., East Lansing, MI; [7]Inst. of Biomed. Engin., Karlsruhe Inst. of Technol., Karlsruhe, Germany

**Abstract:** Conductive boron-doped diamond is a versatile material that has been shown to have excellent biocompatibility, a wide working potential window in aqueous solutions, and has shown to be an excellent material to study electrochemical systems. Boron-doped diamond microelectrodes have both been previously fabricated by growing diamond on sharpened tungsten wire and we have grown them to be freestanding and utilized to measure dopamine and other electroactive neurotransmitters with high spatial and temporal resolution using fast-scan cyclic voltammetry (FSCV). Here we report on the further development and optimization of boron-doped diamond electrodes to feature an all-diamond microelectrode, grown as a solid core that can electrochemically measure common neurotransmitters using FSCV and showcase a linear dynamic response. These boron-doped microelectrodes (BDDME) are rectangular in structure, with a cleaved planar tip for electrochemical sensing. Using these electrodes, we explored the effects of laser treating the diamond surface, comparing a raw cleaved diamond to that which was cleaved using a femtosecond visible laser and microsecond infrared laser. We

also characterized the effect of two common electrodeposited polymers, PEDOT:PSS and PEDOT:Nafion, and the influence on the electrodes sensitivity to both dopamine, serotonin as well as pH changes. Here, we characterized the neurotransmitters, linear dynamic range, detection limit, and noise using FSCV. Using all-diamond electrodes for neurotransmitter analysis is advantageous as it is the gateway to wafer batch fabrication of microelectrodes, decreasing errors generated in the traditional hand fabrication methods, and building towards a scalable batch method for electrode array technologies.

**Disclosures:** **J.R. Siegenthaler:** None. **B. Kepros:** None. **N.J. Lorenz:** None. **V. Örnbratt:** None. **J.B. Landgraf:** None. **B. Gupta:** None. **M.L. Perillo:** None. **R. Rechenberg:** None. **G.H.U. Banna:** None. **D. Galstyan:** None. **A. Hardy:** None. **M.F. Becker:** None. **E.K. Purcell:** None. **W. Li:** None.

**Poster**

**PSTR057. Neuromodulation Techniques: Electrical, Magnetic, Thermal, Optical, and Optogenetics**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR057.14/Web Only

**Topic:** I.07. Data Analysis and Statistics

**Support:** Conahcyt
UAM-Izt
HIMFG

**Title:** Magnetic resonace spectroscopy and brain volumetry in children with post severe covid infection

**Authors: *B. MACIAS, Jr**[1], A. AMADO[2], P. SUAREZ[3], E. BARRAGAN[2], B. DE CELIS[5], J. GARCIA[2], C. MAURICIO[4], S. BONILLA[4], M. ROMERO FLORES[2], S. HIDALGO TOBON[3]; [1]fisica, uam iztapalapa, México, Mexico; [2]Ped. Neurol, [3]Imageology, [4]Covid, HIMFG, CDMX, Mexico; [5]Fac. Phys.-Math. Sci., BUAP, Puebla, Mexico

**Abstract:** Spectroscopy and volumetric of NMR are non-invasive quantitative imaging techniques for the diagnosis and management of central nervous system disorders. COV19 primarily affects the lower respiratory tract, but it can involve the central nervous system (CNS) [Avantika S. et al. 2021]. Structural analysis based on spectroscopy and volumetric technique to quantify the impact of COV19 on the brains of pediatric patients through alteration of metabolites in the prefrontal cortex and volumetric changes in brain tissues and structures. NMR spectroscopy and volumetric sequences were performed using a 3T SIEMENS Skyra scanner using an eight-channel receive-only head coil at the Children Hospital of México Federico Gómez for patients who were admitted to the hospital after having severe COV19 (n=10, age from 7 to 11 years). The studies were conducted in patients after having severe cov19 and followed up one year later. For single-voxel spectroscopy (SVS) was obtained using a point-

resolved spectroscopy (PRESS) sequence with an interest of 13X13X13 mm3 voxel was located at prefrontal cortex, the parameters were set as TR/TE=2000/135 ms. NMR volumetric T1-weighted 3D gradient-echo volumetric sequence was used, parameters TR/TE = 2200/2.45 ms, flip angle = 8°, acquisition matrix= 256 x 256, slice thickness= 1.2 mm, gap 0mm. FreeSurfer software was used for volumetric, and TARQUIN was used for processing metabolites N-acetyl aspartate (NAA), choline (Cho) and creatine (Cr). Patients data were compared with control patients with no diagnosis of COV19 or other adjacent neurological diagnose; given results of an independent sample t-test in software SPSS, only were accepted p-value < 0.05. MRS results showed alteration in the metabolites NAA and Cr. Volumetric results showed alteration in the left and right lateral ventricles. These results indicate damage in the CNS in post-COV19 pediatric patients, characterized by neuronal impairment and tissue damage.

**Disclosures:** **B. Macias:** None. **A. Amado:** None. **P. Suarez:** None. **E. Barragan:** None. **B. de Celis:** None. **J. Garcia:** None. **C. Mauricio:** None. **S. Bonilla:** None. **M. Romero Flores:** None. **S. Hidalgo Tobon:** None.

**Poster**

**PSTR057. Neuromodulation Techniques: Electrical, Magnetic, Thermal, Optical, and Optogenetics**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR057.15/VV60

**Topic:** I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

**Title:** Home cage monitoring as an alternative to traditional CNScore[GT1]battery safety pharmacology assessment: Results of a Multi-Company evaluation of data from three compounds.

**Authors: *D. ARMSTRONG**[1], A. CHERIAN[2], C. GIULIANO[3], I. RAGAN[4], A. MILNE[5], J. SUTHERLAND[6], M. ROLF[3], G. TEUNS[7], F. PIBIRI[8], E. ROSSMAN[2], M. MCCLAFFERTY[2], R. SILLITO[9], A. HOLMES[4];
[1]Univ. of Edinburgh, Edinburgh, United Kingdom; [2]GSK, Collegeville, PA; [3]AstraZeneca, Cambridge, United Kingdom; [4]NC3Rs UK, London, United Kingdom; [5]Icon Plc, Livingston, United Kingdom; [6]CRL Labs., Edinburgh, United Kingdom; [7]Global Safety Pharmacol., Janssen Res. Fndn., Vosselaar, Belgium; [8]Jaasen, Beerse, Belgium; [9]Actual Analytics Ltd, Edinburgh, United Kingdom

**Abstract:** CNS safety pharmacology assessment is included in the core battery assessment of vital organ functions in the ICH S7A guidelines and traditionally relies on the FOB/Irwin, conducted in rodents. FOB/Irwin is a subjective behavioural screen including a panoply of rodent-specific parameters that are sometimes difficult to translate to human outcomes. Home cage monitoring objectively measures continuous rodent behavior, day and night, over multiple days. The welfare benefits of the approach which allows group housing and non-invasive monitoring are established. However, how these data compare to those obtained in the

FOB/Irwin remains largely untested in CNS safety testing. Here we assessed the potential of rodent home cage monitoring to predict risk over traditional FOB/Irwin, using preclinical and clinical data from three compounds for which adverse effects have previously been reported. Hans Wistar rats were administered with one of the three compounds by a single oral gavage then monitored for up to six days. Dosing with all three compounds induced significant measurable changes in non-evoked behaviour as measured in the home cage when compared to oral gavage controls or indeed the animal's own pre-dose baseline recordings. Responses observed included initial hyperactivity shortly after dosing, changes in climbing behaviour, body temperature and hypoactivity in the hours following dosing in two of the compounds. For two of the compounds, clear behavioural effects were observed at clinically relevant concentrations that were not observed in FOB/Irwin. Moreover, in some cases behavioural effects (a suppression of night time activity) persisted for many days. The continuous behavioural profiles obtained from the homecage monitoring demonstrate the inherent behavioural variability in animals over time and clearly highlight a sampling risk in using snapshot observations of behaviour at arbitrary times. Home cage monitoring represents an animal welfare refinement and could be used in repeat dose toxicology studies alongside clinical observations or in place of FOB/Irwin.

**Disclosures:** **D. Armstrong:** A. Employment/Salary (full or part-time); Actual Analytics Ltd. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Actual Analytics Ltd. **A. Cherian:** None. **C. Giuliano:** None. **I. Ragan:** None. **A. Milne:** None. **J. Sutherland:** None. **M. Rolf:** None. **G. Teuns:** None. **F. Pibiri:** None. **E. Rossman:** None. **M. McClafferty:** None. **R. Sillito:** A. Employment/Salary (full or part-time); Actual Analytics Ltd. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Actual Analytics Ltd. **A. Holmes:** None.

**Poster**

**PSTR057. Neuromodulation Techniques: Electrical, Magnetic, Thermal, Optical, and Optogenetics**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR057.16/VV61

**Topic:** G.09. Drugs of Abuse and Addiction

**Support:** NIH Grant DA51100
NIH Grant AI145206

**Title:** Electrochemical aptamer-based biosensors for exploring the relationship between in brain cocaine concentrations and associated behavioral responses

**Authors: *K. M. HONEYWELL**[1], Y. WU[1], Y. WANG[1], O. ALKHAMIS[2], M. H. MCDONOUGH[1], M. K. ERDAL[1], M. R. STOCCO[1], J. GERSON[1], Y. XIAO[2], W. MEIRING[1], J. P. HESPANHA[1], K. W. PLAXCO[1], T. E. KIPPIN[1];
[1]UCSB, Goleta, CA; [2]North Carolina State Univ., Raleigh, NC

**Abstract:** Cocaine addiction remains a major health concern. Despite the attention directed at understanding the molecular mechanisms of drug response, there is a dearth of information on the cocaine concentrations that trigger these physiological processes due to the lack of a tool that can provide appropriate temporal resolution or perform in real-time. Thus motivated, we adopted a generalizable, real-time sensing platform, electrochemical aptamer-based (EAB) biosensors, to the task of in brain monitoring molecules in awake, freely behaving animals. Here, we report a novel EAB biosensor that exhibits appropriate sensitivity and temporal resolution (~ 15 s) to fully resolve the pharmacokinetics of cocaine in the brains of rats. These data combined with standard behavioral measurements enable detailed analyses of the relations between in brain concentration and behavioral response for individual subjects. In summary, EAB biosensors are capable of determining individual, in brain pharmacokinetics of cocaine in behaving animals that can enable concentration-response, as opposed to dose-response, analyses.

**Disclosures: K.M. Honeywell:** None. **Y. Wu:** None. **Y. Wang:** None. **O. Alkhamis:** None. **M.H. McDonough:** None. **M.K. Erdal:** None. **M.R. Stocco:** None. **J. Gerson:** None. **Y. Xiao:** None. **W. Meiring:** None. **J.P. Hespanha:** None. **K.W. Plaxco:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Diagnostic Biochips, Nutromics. **T.E. Kippin:** None.

**Poster**

**PSTR057. Neuromodulation Techniques: Electrical, Magnetic, Thermal, Optical, and Optogenetics**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR057.17/VV62

**Topic:** I.04. Physiological Methods

**Support:** NIH Grant DP2NS122605
NIH Grant K01EB027184
DoD Grant N00014-23-1-2006
DoD Grant N00014-22-1-2371

**Title:** Microfabricated passive resonators as a next-generation modality for neural recording

**Authors: *J. PHILLIPS**, F. WANG, S. BHATT, E. MASTERSON, A. VAREBERG, I. BOK, T. ZHU, X. REN, A. HAI;
Univ. of Wisconsin-Madison, Madison, WI

**Abstract:** Current methods for sensing brain activity compromise between invasiveness, spatial and temporal precision, and scope. Implanted electrode arrays capable of recording signals from individual neurons or small populations require persistent transcranial wiring to operate, and record activity from limited volumes of tissue. High-coverage modalities such as functional Magnetic Resonance Imaging (fMRI), and in particular the Blood Oxygenation Level Dependent (BOLD) signal, are capable of recording from the whole brain simultaneously and noninvasively.

However, BOLD fMRI is limited spatially by the density of capillaries in the brain and temporally by the delay between activity and increased oxygenation. We present an alternative approach whereby a microfabricated planar inductor-capacitor resonator circuit designed to resonate at MRI frequencies is in contact with a population of neurons, takes advantage of local fluctuations in the concentration of extracellular ions as a variable load resistance to tune and detune its resonance in response to coordinated activity. We microfabricated these devices on glass wafers with paths to contact pads to allow for precise recording of the device, and tested the ability of these devices to detune in response to changes in ionic concentration. We grew electrically active cultures on these devices to demonstrate their sensing capabilities *in vitro*, by comparing their resonance with simultaneous fluorescent calcium recordings. Microfabricated resonators have approximately 200 Ohms DC resistance, and tune and detune within MRI ranges in response to changes in ionic concentration. Devices support healthy, electrically active cultures, and their resonant response correlates with coordinated network activity, as recorded via calcium imaging. These probes use minimal components to sense activity, reducing bulk, complexity, and cost. They can be recorded via a simple antenna and pave the way for injectable passive electronic devices for bidirectional access to the brain.

**Disclosures:** **J. Phillips:** None. **F. Wang:** None. **S. Bhatt:** None. **E. Masterson:** None. **A. Vareberg:** None. **I. Bok:** None. **T. Zhu:** None. **X. Ren:** None. **A. Hai:** None.

**Poster**

**PSTR058. Ultrasound Neuromodulation Techniques**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR058.01/VV63

**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** NIH Grant 5R01NS109885-05

**Title:** Direct two-photon imaging of focal and cell-type-selective ultrasonic cortical neuromodulation

**Authors:** ***T. LEMAIRE**[1], Y. YUAN[2], A. M. LEMESSURIER[1], J. P. LITTLE[1], R. C. FROEMKE[1], S. SHOHAM[1];
[1]Neurosci. Inst., New York Univ. Grossman Sch. of Med., New York, NY; [2]Yanshan Univ., Yanshan Univ., Hebei, China

**Abstract:** Ultrasonic neuromodulation offers the unique ability to perturb brain circuits in a noninvasive, focal and reversible manner. Yet, the underlying mechanisms by which ultrasound interacts with heterogenous neuron populations to induce functional and behavioral effects, as well as the dependency of these effects on stimulation parameters, remain unclear. These limitations pose a significant challenge for the development of efficient, target- and application-specific sonication protocols.To address this limitation, we developed an experimental platform allowing the simultaneous and co-axial delivery of highly focalized ultrasonic perturbations and

two-photon imaging of direct, single-neuron functional effects in awake head-fixed mice. With this platform, we imaged functional responses evoked by ultrasound in distinct neuronal populations of the visual cortex, using transgenic lines expressing the GCaMP6s fluorescent reporter under a cell-type-specific promoter. We measured and carefully analyzed evoked effects at different ultrasonic peak pressures amplitudes (0-0.8 MPa) and sonication duty cycles (5-80%).Our data shows that low-frequency ultrasound (2.1 MHz) evokes robust responses in local cortical circuits, exciting >40% of the observable Thy1-positive pyramidal excitatory neurons and >80% of observable somatostatin (SST)-positive inhibitory interneurons. Their response magnitude increased monotonically with supra-threshold intensity within the measured range. In contrast, their duty-cycle dependence was not monotonic and saturated at specific duty cycles around 50-70%. Moreover, shifting the acoustic focus away from the imaged region eliminated these responses, thereby confirming the causal dependence of observed effects on the ultrasonic drive.These results constitute a first evidence of the direct in vivo cell-type-selectivity of ultrasound effects in the mammalian cortex. As such, they provide a valuable framework to interpret the circuit mechanisms of ultrasound cortical neuromodulation and predict parameter-dependent neuromodulatory effects.

**Disclosures:** **T. Lemaire:** None. **Y. Yuan:** None. **A.M. Lemessurier:** None. **J.P. Little:** None. **R.C. Froemke:** None. **S. Shoham:** None.

**Poster**

**PSTR058. Ultrasound Neuromodulation Techniques**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR058.02/VV64

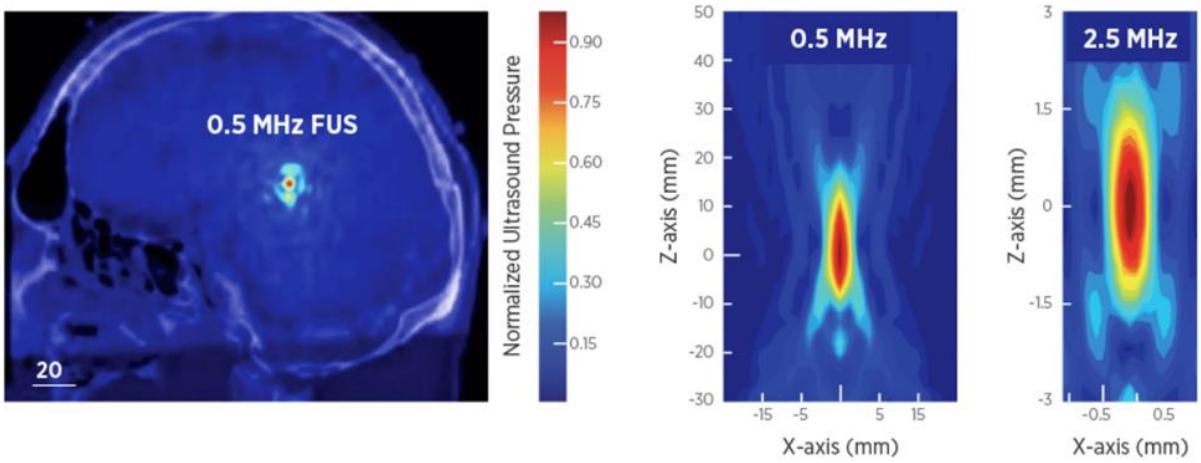
**Topic:** I.08. Methods to Modulate Neural Activity

**Title:** Dynamic transcranial ultrasound to modulate human mood, behavior, and cognition by targeting cortical and deep-brain regions using NeuroFUS

**Authors: *K. P. MORRISON**[1], W. TYLER[2];
[1]Sonic Concepts, Inc., Bothell, WA; [2]Biomed. Engneering, Univ. of Alabama, Birmingham, AL

**Abstract:** Neuromodulation is defined as reversible stimulation or inhibition of neuronal activity. Neuromodulation of brain activity is known to affect mood, memory, and cognition and is accomplished using several techniques including chemical, thermal, electrical, and magnetic. Noninvasive methods, such as transcranial electrical (tES) and magnetic (TMS) stimulation is used to treat clinical depression, memory loss, and other neurocognitive disorders. However, these methods deliver diffuse stimuli across the brain, and neither offer precise targeting nor reaches deep brain regions. As with tES or TMS, transcranial focused ultrasound (tFUS) stimulation uses external wave frequencies to affect neuronal activity in the brain or peripherals. Instead of more diffuse electric or magnetic stimuli, tFUS uses short bursts of finely tuned low-intensity sound waves that concentrate at precise targets in the brain. The resolution of peak electric field strengths produced by TMS extends up to centimeters in some directions. By

contrast, tFUS modulates brain activity with millimeter spatial resolution. The tFUS delivery method confers high spatial resolutions and is readily compatible with other human neuroscience methods, such as behavior, EEG, and fMRI. Sonic Concepts' NeuroFUS® is used in laboratories around the world for conditions such as depression, epilepsy, memory, aging disorders, pain, OCD, substance use disorder, orthostatic tremor, schizophrenia, stroke, traumatic brain injury, and more. Changes in patient and human subject outcomes following NeuroFUS® treatments imply that continued research in tFUS for deep brain neuromodulation is warranted. Following tFUS, a significant recovery from minimally conscious states for patients with disorders of consciousness, improvements in memory and verbal processing in Alzheimer patients, and an overall increase in happiness and decrease in anxiety in patients with depression have been observed. NeuroFUS is shown to be generally safe with no serious adverse effects, even at ultrasound intensities higher than FDA limitations.




**Disclosures:** **K.P. Morrison:** None. **W. Tyler:** None.

**Poster**

**PSTR058. Ultrasound Neuromodulation Techniques**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR058.03/WW1

**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** NIH Grant EB028319

**Title:** The impact of focused ultrasound neuromodulation on cortical microvascular flow in vivo

**Authors: *Y. SHEN**[1], J. V. JETHE[1], J. HEHIR[1], C. REN[2], S. HAO[2], M. AMARAL[2], C. ZHOU[2], J. A. N. FISHER[1];
[1]Physiol., New York Med. Col., Valhalla, NY; [2]Washington Univ. in St. Louis, St. Louis, MO

**Abstract: The impact of focused ultrasound neuromodulation on cortical microvascular flow in vivo**

Yubing Shen, Jyoti V Jethe, Jacob Hehir, Marcello Amaral, Chao Ren, Senyue Hao, Chao Zhou, and Jonathan A. N. Fisher

Low intensity focused ultrasound (FUS) is a promising new technology for non-invasive neuromodulation. Unlike other modalities, FUS offers the potential for submillimeter-scale spatial resolution both superficially at the cortex as well as in deep brain structures. However, FUS induces effects on the nervous system that are complex and unfold over both short and longer timescales. Preclinical studies attempting to dissect the mechanisms of FUS neuromodulation have focused largely on effects in neurons; however, the prolonged timescale of effects suggests the involvement of vasculature as well. Functional magnetic resonance imaging (fMRI) and laser speckle investigations have demonstrated that FUS induces hemodynamic activity in the cortical vasculature. Those measurements, though, have at best resolved flow in larger vessels. We aimed to explore the impact of FUS at the level of the cortical microvasculature, where there is a direct interplay between neuronal and vascular function. To that end, we used optical coherence tomography angiography (OCT-A) to explore the effects of FUS on microvascular flow within the somatosensory cortex of mice in vivo. Our custom hybrid OCT-A system has < 3.5 um lateral resolution and features an FUS ring transducer whose focus is co-localized with the optical focus. The mechanical effect varied depending on the targeted brain region and stimulation parameters. At FUS intensities of 10W/cm$^2$ ($I_{sppa}$), we observed vasodilation and increased blood flow in vessels of diameters ranging from 5-20 um. These effects persisted at least 10 minutes post FUS. We additionally measured the impact on microvascular flow following multiple doses of FUS. Finally, through immunohistochemical investigation, we confirmed that sonication did not damage tissue at the FUS intensities used in our experiments. Our results indicate that sonication exerts effects not only on neuronal function, which has been extensively studied, but also at the level of microvascular blood flow. Future investigation can help resolve the relative contributions of neuronal and vascular effects underlying acute and prolonged neuromodulation effects of FUS.

**Disclosures: Y. Shen:** None. **J.V. Jethe:** None. **J. Hehir:** None. **C. Ren:** None. **S. Hao:** None. **M. Amaral:** None. **C. Zhou:** None. **J.A.N. Fisher:** None.

**Poster**

**PSTR058. Ultrasound Neuromodulation Techniques**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR058.04/WW2

**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** DARPA KeyStone
FDA DBP

**Title:** Low frequency ultrasound induced neural responses in the mouse brain

**Authors:** L. SHI[1], C. MASTRACCHIO[1], J. KENT[1], G. K. WU[2], ***M. YE**[1];
[1]FDA, Silver Spring, MD; [2]US Food and Drug Admin., U.S. Food and Drug Admin., Silver Spring, MD

**Abstract:** Although the neuromodulation effect of >250 kHz ultrasound has been extensively demonstrated, the impact of low-frequency ultrasound, which can be air transduced and less attenuated by the skull, on the central nervous system remains inconclusive. This study aims to elucidate the potential biophysical impact of low-frequency ultrasound on the central nervous system by investigating in vivo and in vitro cortical neuronal responses to pulsed 40 kHz ultrasound using calcium imaging and electrophysiology in mice. Our results indicate a dose-dependent relationship, with increased responses observed at higher duty cycles in the somatosensory cortex. However, in vitro brain slice studies revealed minimal neural responses in the somatosensory cortical region, suggesting that the observed effects may be attributed to indirect network effects. Furthermore, we explored the influence of isoflurane and ketamine on neural responses to ultrasound. Notably, ketamine was found to block neuronal responses, suggesting a possible involvement of the NMDA receptor in the signaling pathway. This research unveiled the potential effects of low-frequency ultrasound on the central nervous system, opening a new avenue for future neuromodulation research in this field. **Disclaimer:** The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services. The findings and conclusions in this article have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any Agency determination or policy. This article reflects the views of the authors and should not be construed to represent the FDA's views or policies. **Acknowledgement:** This study was supported by the Defense Advanced Research Projects Agency KeyStone Program and internal funding from Division of Biomedical Physics, Office of Science and Engineering Laboratories, Center for Devices and Radiological Health of the U.S. Food and Drug Administration (FDA). This project was supported in part by an appointment to the science education programs at the FDA, administered by Oak Ridge Associated Universities through the U.S. Department of Energy Oak Ridge Institute for Science and Education. **Distribution Statement:** 'A' (Approved for Public Release, Distribution Unlimited)

**Disclosures: L. Shi:** None. **C. Mastracchio:** None. **J. Kent:** None. **G.K. Wu:** None. **M. Ye:** None.

**Poster**

**PSTR058. Ultrasound Neuromodulation Techniques**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR058.05/WW3

**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** NIH RF1 NS126144

**Title:** Neuromodulation of Tactile Responses in the Primate Secondary Somatosensory Cortex Using Focused Ultrasound

**Authors: *N. ZHENG**[1,2], M. A. PHIPPS[2], A. T. NEWTON[2,3], P. F. YANG[2,3], M. K. SIGONA[2,4], C. F. CASKEY[2,3], L. CHEN[2,3];
[1]Vanderbilt Univ. Med. Ctr., Nashville, TN; [2]Vanderbilt Univ. Inst. of Imaging Sci., Nashville, TN; [3]Dept. of Radiology and Radiological Sciences, Vanderbilt Univ. Med. Ctr., Nashville, TN; [4]Dept. of Biomed. Engineering, Vanderbilt Univ., Nashville, TN

**Abstract:** Transcranial focused ultrasound (FUS) stimulation combined with functional MRI (fMRI) monitoring, offers a precise, noninvasive technology for dissecting functional brain circuits. This technology has potential as a therapeutic strategy for neurological and psychiatric disorders by modulating altered brain functional networks. Our previous studies have shown that pulsed wave (PW) focused ultrasound at moderate intensities bidirectionally modulated (both excitatory and inhibitory) neural activity in the somatosensory area 3a/3b and their associated networks both in resting state and active state, as observed through BOLD fMRI. It has been proposed that applying continuous wave (CW) FUS can eliminate auditory confound caused by auditory frequencies contained in PW stimulation while exerting neuromodulation effects. In this study, we aim to investigate the effect of CW FUS at moderate intensities on the secondary somatosensory cortex (S2) in macaque monkey. We employed optical tracking outside the MRI scanner to guide FUS beam placement to the targeted S2 hand tactile region, which was pre-defined by fMRI. Before the fMRI scanning, the location and actual delivery of FUS were confirmed using MR-acoustic radiation force imaging. During the fMRI data acquisition, three conditions were randomly presented: tactile stimulation alone, CW FUS alone, and simultaneous presentation of tactile stimulation and CW FUS. FUS (650 kHz, 550 kPa estimated *in situ*, 250 ms every 2 s with 50 us linear ramp) was delivered in a block-based scheme identical to the tactile stimuli, in a cycle of 16 seconds on and 30 seconds off. Our results showed that no significant fMRI activation was observed in S2 or auditory circuits when CW FUS was delivered alone. This finding indicates that CW FUS exerts minimal effect on resting neurons and appears to differ from the effects observed with PW FUS. However, the concurrent delivery of CW FUS effectively suppressed the fMRI signals elicited by tactile stimulation, which aligns with our previous observations using PW FUS and suggests that both PW and CW FUS at moderate intensities suppress neural activity of tactile responded neurons. In summary, our study has demonstrated the neuromodulatory effects of CW FUS on the target S2. By attenuating auditory side effects, CW FUS coupled with fMRI shows promise as a valuable tool for dissecting brain circuits and probing causal functional connections.

**Disclosures: N. Zheng:** None. **M.A. Phipps:** None. **A.T. Newton:** None. **P.F. Yang:** None. **M.K. Sigona:** None. **C.F. Caskey:** None. **L. Chen:** None.

**Poster**

**PSTR058. Ultrasound Neuromodulation Techniques**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR058.06/WW4

**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** NIH R01 NS124564

**Title:** Transcranial Focused Ultrasound Modulating Time-locked and Delayed Neuronal Activities

**Authors: *H. GAO**, S. RAMACHANDRAN, K. YU, B. HE;
Carnegie Mellon Univ., Pittsburgh, PA

**Abstract:** Low-intensity transcranial focused ultrasound (tFUS) has shown unequal modulation effects on neuronal subpopulations. Previous studies demonstrated that tFUS could elicit excitatory effects in regular-spiking units (RSUs) during sonication with specific parameters. However, to understand the potential sustained neural effects, post-sonication effects on neural activities need to be investigated. In this study, we aimed to explore the responses of different neuronal types to tFUS, both during sonication and after sonication. We applied the 128-element random array ultrasound transducer H276 (*f*0: 1.5MHz) to stimulate the somatosensory cortex (S1) of anesthetized wild-type rats (n=18). Multi-unit activities (MUAs) and local field potentials (LFPs) were recorded to determine the modulation effects of neural activities at different parameters through multi-channel intracranial electrophysiological recordings. The MUAs were separated into RSUs and fast-spiking units (FSUs) based on their action potential waveforms. Our findings revealed that LFP waveforms were sensitive to ultrasound pulse repetition frequency (PRF). Differences in LFP amplitudes among PRF conditions occurred from tFUS onset to 0.7s post-sonication, which indicated both time-locked and delayed response of neural activities to tFUS. Further, we found during sonication, RSUs exhibited significant excitatory responses to high PRFs compared to those in low PRFs while FSUs did not show any response to the change of PRFs. After sonication, both neuronal types displayed increased activities at high PRFs. We also found pulse duration (i.e., 100μs, 200μs, 400μs) showed no impact on time-locked neuronal response and FSUs' delayed response. While in PRF 3000 Hz and PRF 4500 Hz, shorter pulse duration induced higher delayed response of RSUs. This work demonstrates the different responses of neuron types during sonication and after sonication with specific PRFs and pulse durations, extending previous studies by providing an exploration of the sustained effect of tFUS on neuronal subpopulation activities.

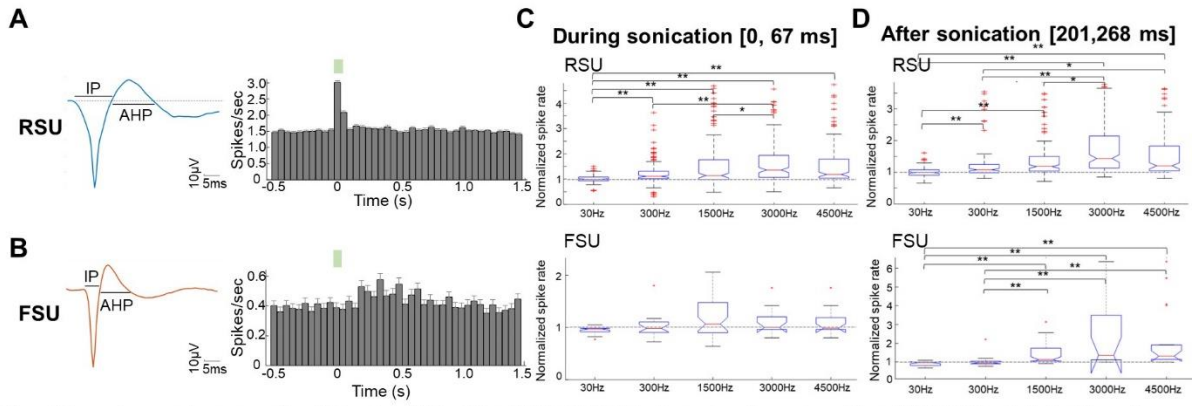



Figure 1 Unequal neuronal responses of an RSU and an FSU to different PRFs. **(A-B)** Typical examples of a regular-spiking unit (RSU) **(A)** and a fast-spiking unit (FSU) **(B)** to tFUS with PRF 1500Hz. (Left) The temporal features of action potential waveforms. (Right) Representative peri-stimulus time histograms (PSTHs, bin size: 50ms, n=500 trials for each time bin). **(C-D)** Normalized firing rates of RSUs (upper) and FSUs (bottom) vs. the PRFs during sonication**(C)** and after sonication **(D)**.

**Disclosures:** **H. Gao:** None. **S. Ramachandran:** None. **K. Yu:** None. **B. He:** None.

**Poster**

**PSTR058. Ultrasound Neuromodulation Techniques**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR058.07/WW5

**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** NIH NS124564
EB029354

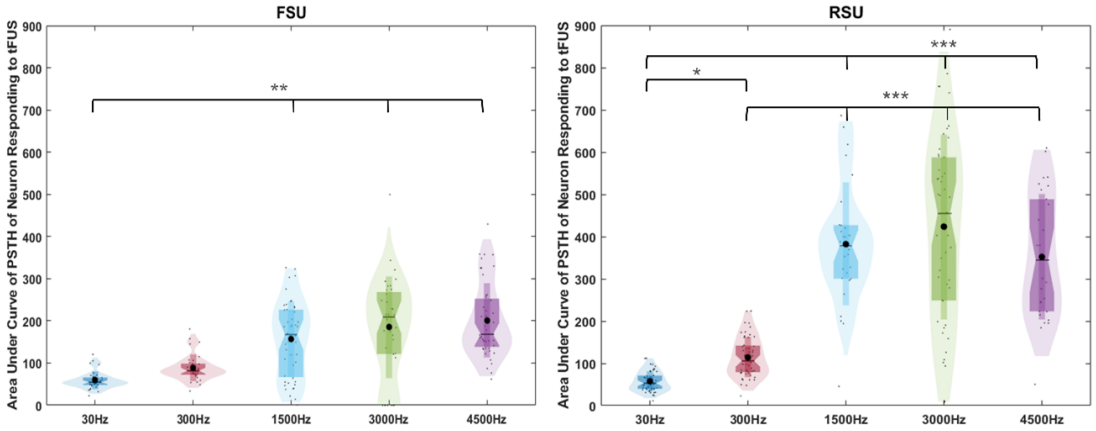
**Title:** An awake-head fixed rat model for the characterization of neuronal responses to transcranial focused ultrasound stimulation

**Authors:** ***S. RAMACHANDRAN**, H. GAO, K. YU, B. HE;
Carnegie Mellon Univ., Pittsburgh, PA

**Abstract:** Transcranial focused ultrasound (tFUS) is a neuromodulatory technique of growing interest to neuroscience research due to its noninvasive ability to stimulate the brain with high spatial specificity. Research has shown tFUS can modulate neural activity and has shown cell-type specific variance in responses, but many of these studies are confounded by the use of anesthesia, which may interfere with effects. In order to fully characterize the effects of tFUS, eliminating this confound is critical. In this study, we develop an awake head-fixed model of HSD: WI rats, compatible with the 128-element random array ultrasound transducer H276 ($f_0$: 1.5 MHz, axial specificity: 1.36 mm, lateral specificity: 0.46 mm), allowing us to target the awake rat with tFUS while recording local field potential (LFP) and multi-unit activity (MUA) from chronically implanted Neuronexus electrodes (32-channel). Designs for the headpiece were improved iteratively, and rats were trained for head fixation. We then stimulated the rat S1 with tFUS with pulse repetition frequencies (PRFs) of 30 Hz, 300 Hz, 1500 Hz, 3000 Hz, and 4500

Hz, with pulse duration of 100 µs and sonication duration of 67 ms. Initial data include 3 recordings each from 2 adult male rats, and spike sorting resulted in 30-50 neurons of fast-spiking units and regular spiking units per condition. Clear responses to ultrasound stimulation were observed in PSTH plots. As in anesthetized models, RSUs show a positive relationship to the increasing PRF with significant differences in responses, while FSUs show a weaker relationship. This study confirms the cell-type specific responses to ultrasound PRF, and provides a highly needed platform for future investigations of ultrasound neuromodulation in an awake rat model.

Figure 1: Violin plots of neuronal responses to tFUS with varying PRFs, split into FSUs and RSUs.




**Disclosures:** **S. Ramachandran:** None. **H. Gao:** None. **K. Yu:** None. **B. He:** None.

**Poster**

**PSTR058. Ultrasound Neuromodulation Techniques**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR058.08/WW6

**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** Swiss National Science Foundation

**Title:** Ultrasound neuromodulation of peripheral fibers using a microfabricated nerve-on-a-chip platform

**Authors:** ***E. VICARI**[1], T. LEMAIRE[1,2], V. PAGGI[1], O. RIZZO[1], E. NEUFELD[3], S. LACOUR[1], S. MICERA[1,4];
[1]Neuro-X Inst., EPFL, Genève, Switzerland; [2]New York Univ., New York, NY; [3]IT'IS Fndn., Zurich, Switzerland; [4]Scuola Superiore Sant'Anna, Pisa, Italy

**Abstract:** Focused ultrasound (FUS) is increasingly recognized as a promising non-invasive neuromodulation modality. While its use in modulating brain circuits is well-established, its

application to peripheral nerves remains limited and under debate. This study aims to characterize FUS-evoked responses in isolated peripheral neural fascicles and elucidate its capability to induce a consistent firing behavior. Our objective is to confirm the potential of FUS for peripheral neuromodulation and guide the development of effective sonication protocols.
In this study, we used an ex vivo experimental setup to alternatively apply electrical or ultrasonic stimuli to neural fascicles and record the evoked neural activity. Nerve fascicles, isolated from explanted rat spinal roots, were placed in a microfabricated nerve-on-a-chip platform (Gribi et al., 2018) featuring two aligned microchannels with microelectrodes for electrical stimulation and recording. Acoustic stimulation was delivered using a FUS transducer (500 kHz central frequency) positioned above the fascicle. The sonication protocol consisted of single or repeated pulses of varying peak pressure amplitude and pulse duration. Using this experimental setup, we recorded propagating compound action potentials (CAPs) initiated by both electrical and ultrasonic stimuli along the fascicle. We also tested different experimental conditions to provide insights into the interaction mechanism between FUS and the neural membrane.
Our findings show that within an optimized parametric regime, single-pulse ultrasound stimulation consistently elicits neural responses that are similar in shape and amplitude to those evoked electrically. Clear strength-duration excitability patterns emerged when exploring the stimulation parameter space defined by ultrasound peak amplitude and pulse duration. Moreover, by exploiting the propagation properties of the evoked responses, we differentiated the responses from different fiber types and characterized their recruitment properties. Finally, we found that repeated FUS pulses can induce multiple successive neural responses.
This comprehensive characterization of FUS-evoked responses in isolated neural fascicles confirms that FUS stimulation can directly excite peripheral nerve fibers. It also unveils optimal stimulation parameters, which are fundamental for further investigations. Furthermore, this study demonstrated the capability of FUS to induce a sustained firing behavior, suggesting promising clinical neuromodulation applications.

**Disclosures:** **E. Vicari:** None. **T. Lemaire:** None. **V. Paggi:** None. **O. Rizzo:** None. **E. Neufeld:** None. **S. Lacour:** None. **S. Micera:** None.

**Poster**

**PSTR058. Ultrasound Neuromodulation Techniques**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR058.09/WW7

**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** Hong Kong Research Grants Council General Research Fund (15104520, 15102417 and 15326416)
Hong Kong Innovation Technology Fund (MRP/018/18X and MHP/014/19)
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Key-Area Research and Development Program of Guangdong Province

(2018B030331001)
internal funding from the Hong Kong Polytechnic University (1-ZVW8 and 1-CD76)
Guangdong High Level Innovation Research Institute (2021B0909050004)

**Title:** Endogenous mechanosensation constraints on in vivo sonogenetic modulation

**Authors: *Q. XIAN**[1], Z. QIU[2], D. LI[1], T. LEI[1], X. HOU[1], L. SUN[1];
[1]Biomed. Engin. Dept., The Hong Kong Polytechnic Univ., Hong Kong, China; [2]Guangdong Inst. of Intelligence Sci. and Technol., Guangdong Inst. of Intelligence Sci. and Technol., Zhuhai, China

**Abstract:** Manipulating specific neural activity by physical intervention is a powerful method to gain causal insight into brain functions and treat brains disorders. Sonogenetics, analogous to optogenetics, combining the targeted expression of mechanosensitive cellular machineries and precise delivery of ultrasound, has been shown to offer the prospect of non-invasive stimulation, high spatiotemporal resolution, accurate deep brain targeting through cell-type specific gene expression, and high potential clinical translation. However, during sonogenetics experiment, we found an “interesting phenomenon” that the mice show aversive response to sonication when certain brain regions were stimulated. It is essential to understand what the possible causes (such as auditory confound, endogenous ultrasound sensitivity) of this aversive phenomenon are and how to minimize it to optimize this technique. We applied ultrasound stimulation to mice, screened c-fos expression of the whole brain, and found that neural activities of different brain regions under sonication showed different levels of response. Specifically, ultrasound stimulation can significantly increase the neural activity of the somatosensory cortex, which is responsible for receiving and processing sensory information from the body, and participate in aversive emotional learning. We believe the activation of somatosensory cortex by ultrasound involves in the US induced animal aversive response. We conducted fiber photometry experiments and whisker movement experiments to show that auditory effect was not the main contributor. In addition, ex-vivo patch clamp experiments show sonication can induce an inward current, indicates that endogenous mechanical ion channels play role in this activation. In sonogenetic experiment, ultrasound sensitive ion channels showed larger capability to enhance the cell sensation to ultrasound stimulation compared to control group. To minimize the aversive or other responses, it is importance to understand the mechanosensation of targeted region.Altogether, we conclude that different brain regions sense and respond to FUS differently. Sonogenetic method can selectively manipulate the brain region that already have a background response to ultrasound to activate neurons and affect distinct behaviors. Importantly, the local field mechanosensation in different regions should be considered in further ultrasound neuromodulation study. Developing more sensitive ultrasound sensitive ion channel and optimizing the ultrasound parameters are needed to improve the potential application value of sonogenetic method in research and clinic.

**Disclosures:** **Q. Xian:** None. **Z. Qiu:** None. **D. Li:** None. **T. Lei:** None. **X. Hou:** None. **L. Sun:** None.

**Poster**

**PSTR058. Ultrasound Neuromodulation Techniques**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR058.10/WW8

**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** NIH BRAIN INITIATIVE R01NS112152

**Title:** A method for recording ultrasonic neuromodulation of single cells in mouse hippocampal slices with a perforated multi-electrode array (pMEA)

**Authors: *M. MENZ**, S. BACCUS;
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**Abstract:** Ultrasonic neuromodulation has potential both in basic research and clinical therapy, and can penetrate non-invasively deep into brain tissue with high spatiotemporal resolution. However, fundamental mechanistic questions remain unanswered, including which cell types and ion channels are affected, and how direct cellular effects can be distinguished from network effects. The relationship between stimulus protocols and mechanisms is also unknown, and there exists a large range of parameters including intensity, frequency, duty cycle and more complex pulse patterns. An important aspect of ex vivo experiments is to maintain tissue stability in order to explore the large stimulus parameter space. The pMEA (Multichannel Systems) applies a secondary perfusion system that uses a highly controlled vacuum from below to promote close contact with electrodes, and also perfuses solution through the slice to maintain the health of cells close to the MEA. An additional benefit is the reduction of standing waves present with conventional MEAs, known to influence ultrasonic neurostimulation. We recorded from p25-p42 mice of both sexes at 1 MHz. At this frequency, even at relatively high intensities, we did not observe evoked responses from ultrasound stimulation alone. However, by applying electrical stimuli through selected pMEA electrodes to stimulate the Schaffer collaterals, we found that ultrasound modulates the electrically evoked response. Based on previous experiments, we applied 0.2 ms electrical stimuli at the end of a 100 ms ultrasonic continuous wave pulse, which allowed an optimal measurement of ultrasound effects. Stimuli were delivered every 10 s over 75 minutes with 90 trials of five ultrasound intensities randomly shuffled between 0 and 6.4 $W/cm^2$. Typically 20-30 cells were recorded, distributed between CA1, CA3 and DG. About 50% of cells increase their activity in response to either electrical or electrical with ultrasonic stimulation. The addition of ultrasound caused both increases and decreases in electrically evoked responses in all three regions, indicating both excitatory and inhibitory modulatory effects. Of the intensities tested, 0.4 $W/cm^2$ was most effective, tending to increase firing, whereas 6.4 $W/cm^2$ tended to decrease firing consistent with a lower threshold for excitatory ion channels. When combined with pharmacological effects on ion channels or mechanical manipulations of circuit pathways, the pMEA with electrical stimulation is a promising method to study cellular and network effects of ultrasound in different regions of a neural circuit, essential to determining the mechanisms of ultrasonic neuromodulation.

**Disclosures: M. Menz:** None. **S. Baccus:** None.

**Poster**

**PSTR058. Ultrasound Neuromodulation Techniques**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR058.11/WW9

**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** NIH Grant R01NS078168

**Title:** Transparent ultrasound transducer as a cranial window allows neuromodulation and simultaneous multimodal optical brain imaging in awake mice

**Authors: *S. MIRG**[1,2], K. TURNER[4], H. CHEN[2], N. DOODY[2], N. CROWLEY[2], P. J. DREW[3], S.-R. KOTHAPALLI[3];
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**Abstract:** Low-intensity ultrasound neuromodulation is a promising technique for non-invasively modulating neural activity. In vitro and in vivo studies have shown that ultrasound interacts with cell membranes and mechanosensitive ion channels to achieve its modulatory effects. However, the precise mechanisms by which ultrasound acts on different neurons under varying parameters remain poorly understood. This knowledge gap is partly attributed to the technical difficulties of integrating advanced optical molecular imaging techniques with conventional opaque ultrasound transducers. To address this challenge, we propose the use of our recently developed lithium niobate transparent ultrasound thinned skull cranial window for ultrasound stimulation and multimodal optical imaging in awake mice. This innovative approach allows us to stimulate the somatosensory cortex of the awake mice brain through ultrasound while simultaneously imaging using intrinsic optical signal and widefield calcium imaging to derive hemodynamic and neural activity changes, respectively. The implanted ultrasound transducer had a center frequency of 11.2 MHz, and the applied stimulation parameters resulted in a minimal temperature increase of less than 1.2 $^{o}$C. During the stimulation and imaging of the awake mice brain, we observed a decrease in neural activity accompanied by an increase in total blood volume within the stimulated region. These findings demonstrate the feasibility of our stimulation platform for ultrasound neuromodulation and simultaneous multimodal optical imaging. Moreover, this integrated platform opens avenues to further our understanding of the mechanisms underlying ultrasound neuromodulation and can pave the way for its clinical translation.

**Disclosures: S. Mirg:** None. **K. Turner:** None. **H. Chen:** None. **N. Doody:** None. **N. Crowley:** None. **P.J. Drew:** None. **S. Kothapalli:** None.

**Poster**

**PSTR058. Ultrasound Neuromodulation Techniques**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR058.12/WW10

**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** NIH Maximizing Investigator's Research Award (1R35GM147408)
University of Texas at Austin Startup Fund
Robert A. Welsh Foundation Grant (No. F-2084-20210327)

**Title:** Sono-optogenetic deep brain stimulation via self-amplifying liposomal nano transducer

**Authors: *K. TANG**[1], W. WANG[1], I. PIATNITSKII[1], X. LIU[1], X. SHI[2], L. FENNO[3], V. P. BUCH[4], H. WANG[1];
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**Abstract:** Advancements in optogenetics has become instrumental in neuroscience research and treatment of neurological disorders. However, the efficacy of spatio-temporal specific targeting using light due to poor tissue depth penetration and light diffusion requiring the need of invasive fiber optic implants. Recently, minimally invasive sono-optogenetics using focused ultrasound (FUS) demonstrated neural activation based on ultrasound mechanoluminescent nanoparticles but achieved only shallow brain depths due to low ultrasound sensitivity and photon yield. We report a self-amplifying mechanoluminescent nanotransducer based on cascade reactions in liposomes to achieve efficient blue light emission upon ultrasound stimulation. Specifically, chemiluminescence L012, sonosensitizer IR780, and sono-amplifier polyethylene glycol (PEG) 200 coated calcium peroxide (CaO2) nanoparticles were loaded into lipids to prepare the nanotransducer for opsin activation under the FUS stimulation. *In vitro* demonstration of cell-specific sono-optogenetic stimulation in neurons resulted in synchronized firing post-irradiation of ultrasound with around 80% spike probability. We then performed *in vivo* tests in Thy1-ChR2-YFP transgenic mice through local injection of our liposome unilaterally in right M2 region and showed contralateral left limb motion only the experimental groups with all of ChR2, nanoparticles and FUS. The control groups without any one of ChR2, nanoparticles and FUS did not show contralateral left limb motion (n=5 for each group). In addition, we investigated the efficacy in deep photon delivery in Ventral Tegmental Area (VTA) by local injection of our liposome and allowing the mice under self-administered FUS lever press across 5 days to evaluate effects of reward behavioral response under VTA stimulation through sono-optogenetics. Again, rapid increased lever pressing rates was only observed during the days when mice was administered all of ChR2, liposome and FUS. The control groups without any one of ChR2, nanoparticles and FUS did not show increased lever pressing rates (n=4 for each group). Post ad-hoc evaluation of c-Fos signal demonstrated increased neural activation. Additionally, no difference in expression of glial activation or neuron apoptosis was observed after sono-optogenetic stimulation. Overall, our results suggested that our novel liposome nanotransducers enable minimally invasive deep brain stimulation for behavioral control in animals.

**Disclosures:** **K. Tang:** None. **W. Wang:** None. **I. Piatnitskii:** None. **X. Liu:** None. **X. Shi:** None. **L. Fenno:** None. **V.P. Buch:** None. **H. Wang:** None.

**Poster**

**PSTR058. Ultrasound Neuromodulation Techniques**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR058.13/WW11

**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** NIH Grant R21EB028055
NIH Grant R44MH131514

**Title:** Development of focused low-intensity pulsed ultrasound devices as a modulator of neural activity and the foreign body response to implanted cortical electrodes

**Authors: *K. W. GHERES**[1], F. LI[3], J. GALLEGO[3], J. K. GREASER[1], S. J. ILHAM[5], A. F. JAVID[5], O. M. OCON-GROVE[2], K. A. SNOOK[1], R. B. BAGWELL[6], T. D. KOZAI[4], M. U. KIANI[5], M. L. MULVIHILL[1];
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**Abstract:** Trans-cranial focused ultrasound (tFUS) has recently evolved as a spatially confined, non-invasive neuromodulatory method that can be used to regionally excite neurons evoking motor movements, as well as inducing changes in protein expression capable of modulating the cellular response to injury. However, many current tFUS methods rely on large driving electronics and complicated transducer assemblies which are dependent on transmission structures that require non-reusable transmission cones such as poly-vinyl alcohol which limit their widespread adoption. To address this usability gap, we have developed a family of tFUS low intensity pulsed ultrasound (LIPUS) devices with reusable head mounted transducers and miniaturized driving electronics for use in rodent models. We then used these devices to investigate the frequency dependent ability of LIPUS to reduce chronic tissue inflammation associated with implant of silicon microelectrodes and the ability to spatially excite neural activity in cortical motor regions.
Using electrophysiology and two-photon microscopy, our in vivo experiments demonstrate that periodic treatment of electrode site tissue with high frequency (~1MHz) LIPUS reduces microglia activation and extends the longevity of implanted cortical microelectrodes for rodent electrophysiology experiments. We then demonstrate the use of a phased ultrasound array for delivery of low frequency (<800kHz) LIPUS to cortical targets in a rodent model and that the focal plane can be adjusted along a single axis for cortical stimulation along the rostral-caudal plane of cortex.
Our studies demonstrate the validity of tFUS ultrasound for neuromodulation and provide two devices for simplified non-invasive modulation. Our in vivo studies then demonstrate how

periodic application of localized LIPUS to tissue at the neural interface can promote improved electrophysiology signal quality, as measured via signal-to-noise ratios, electrode single-unit yields, and histological evaluation of glial scarring.

**Disclosures:** **K.W. Gheres:** A. Employment/Salary (full or part-time); Actuated Medical Inc. **F. Li:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Actuated Medical Inc. **J. Gallego:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Actuated Medical Inc. **J.K. Greaser:** A. Employment/Salary (full or part-time); Actuated Medical Inc. **S.J. Ilham:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Actuated Medical Inc. **A.F. Javid:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Actuated Medical Inc. **O.M. Ocon-Grove:** A. Employment/Salary (full or part-time); Actuated Medical Inc. **K.A. Snook:** A. Employment/Salary (full or part-time); Actuated Medical Inc. **R.B. Bagwell:** A. Employment/Salary (full or part-time); Actuated Medical Inc. **T.D. Kozai:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Actuated Medical Inc. **M.U. Kiani:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Actuated Medical Inc. **M.L. Mulvihill:** A. Employment/Salary (full or part-time); Actuated Medical Inc.

**Poster**

**PSTR058. Ultrasound Neuromodulation Techniques**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR058.14/WW12

**Topic:** I.08. Methods to Modulate Neural Activity

**Title:** A comparison of the brain response to tactile stimulation with or without ultrasonic stimulation

**Authors: *O. NGWU-HYACINTH**[1], R. WILLOUGHBY[2], M. BOLDING[3];
[1]The Univ. of Alabama at Birmingham, Birmingham, AL; [2]Radiology, Univ. of Alabama, Birmigham, Birmingham, AL; [3]Radiology, Univ. of Alabama At Birmingham, Birmingham, AL

**Abstract:** Ultrasound (US) has emerged as a promising modality to diagnose and treat nervous system disorders noninvasively. However, the effect of US on peripheral nerves (PN) remains controversial. Lele, 1963 showed that US inhibits nerve activity, and an increase in nerve temperature accompanies more suppression of nerve activity. It has also been shown that low-intensity US readily activates non-nerve tissue without direct excitation of the PN (Guo et al., 2022). Considering the immense potential for using US as a noninvasive neuro-modulatory technique, further studies are needed to identify the correct parameters for US neuromodulation. We hypothesised that US applied to a digital nerve will decrease activation of the somatosensory cortex (SSC) in response to tactile stimulation (TS) of the corresponding distal phalanx. Our experiment aimed to find out: (1) if US activates the same brain regions as noninvasive TS of the palmar digital branch of the median nerve, and (2) if US alone could directly modulate tactile-

type response.One male volunteer participated in this study. A 500 kHz focused US transducer was positioned above the median nerve on the middle finger of the left palm and coupled to the palm of the hand with an US gel pad. Functional magnetic resonance imaging (fMRI) was used to estimate neuronal activation in the brain correlated to stimulus timing. Each fMRI run was 8 minutes, and stimuli were presented using a blocked paradigm with 30-second block durations and four block types: baseline blocks with no TS or US stimulation, TS only blocks, US stimulation only blocks, and TS with US blocks. fMRI images were acquired at 3T and data analyzed using FEAT 6.0. Our results show that TS of the median nerve produced bilateral activation in the primary SSC (S1) and secondary SSC (S2). US stimulation produced additional activation in the contralateral superior colliculus and thalamus which is not unusual since these regions integrate somatosensory information and function as a relay for sensory signals, respectively. A possible reason for this discrepancy is that the noninvasive US activates other non-nerve tissue leading to the neurologic sensation of nontactile-type stimuli or involuntary eye movements. To demonstrate the central mechanisms underlying the response to PN stimulation, we integrated PN stimulation with the measurement of changes in brain activity using fMRI. We recommend that more research with increased sample size is warranted to standardize brain regions activated in US stimulation of PN, since this could potentially facilitate the diagnosis of functional neurological deficit.

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**Poster**

**PSTR058. Ultrasound Neuromodulation Techniques**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR058.15/WW13

**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** JSPS KAKENHI Grant Numbers, JP22H05140, JP23H03501
JST FOREST program, JPMJFR2053

**Title:** Neuronal circuit modulation at single-cell level using a focused femtosecond laser

**Authors: *Y. SEGAWA**, K. MASUI, C. HOSOKAWA;
Osaka Metropolitan Univ., Osaka, Japan

**Abstract:** Neuronal networks reorganize their circuits depending on the external stimulus inputs, relating to learning and memory. To reveal the information processing in a brain composed of complex neuronal connections, precise stimulation of neurons is required to identify the modified circuit properties, namely the spatiotemporal dynamics of neuronal spikes. Electrical and pharmacological stimulation are widely utilized as neuronal stimulation methods; however, these methods have tissue invasion and insufficient spatial precision. To modulate neuronal circuit at the single-cell level with less tissue invasiveness, we propose the single-cell stimulation with a focused femtosecond laser. A focused femtosecond laser is advantageous for precise

material processing based on multiphoton absorption at the focal spot. We have previously shown that focusing a femtosecond laser onto the neuronal cell can trigger network-wide neuronal activity. In this study, the electrophysiological properties of single neurons evoked by a focused femtosecond laser were evaluated to determine the effectiveness of neuronal modification at the single-cell level. Hippocampal neurons derived from 18-day-old rat embryos were isolated and cultivated in a glass-bottomed dish for 15—25 days *in vitro*. Neurons were loaded with fluorescence calcium indicator. When a femtosecond Ti: sapphire laser (pulse width ~100 fs, wavelength 800 nm, repetition rate 82 MHz) was focused onto the neuronal cell surface with a microscope objective (60×, N.A. 1.0) for 8 ms of irradiation time, fluorescence intensity drastically increased at the target neuron, indicating extracellular calcium influx due to transient membrane disruption. To investigate the electrophysiological properties of the target neurons, membrane potentials were monitored with whole-cell current clamp recordings. After femtosecond laser irradiation, upstate membrane potentials and highly frequent action potentials were observed. The interspike intervals of action potentials significantly decreased from 440±210 ms (mean±standard deviation, $N = 25$) to 79±65 ms ($N = 127$) within 10 s after laser irradiation. These results suggest that the temporal dynamics of neuronal spikes can be modulated by a focused femtosecond laser. We conclude that focused femtosecond laser stimulation is useful for studying functional connections in neuronal circuits at the single-cell level.

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**PSTR058. Ultrasound Neuromodulation Techniques**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR058.16/WW14

**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** Funding provided by the Palo Alto Veterans Institute for Research (PAVIR)

**Title:** Low-intensity focused ultrasound (LIFU) for the treatment of post-traumatic headache (PTH): a pilot study.

**Authors:** B. C. YOON[1], ***J. P. COETZEE**[2], X. KANG[4], R. BRAR[4,5], M. TIMMERMAN[5], M. M. ADAMSON[3,4];
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**Abstract:** Background: Post-traumatic headache (PTH) is the most common sequelae of traumatic brain injury (TBI). It is hypothesised that the caudate nuclei play an important role in the pathogenesis of headache. In this pilot study, we examined the feasibility, safety, and efficacy of a novel neuromodulation technique, low-intensity focused ultrasound (LIFU), for

precise targeting of heads of caudate nuclei in patients with PTH.
Methods: Two Veterans with persistent, migraine-type PTH from mild TBI were enrolled in this open-label study. Each participant underwent 5 daily LIFU sessions. The first session was performed within MRI with sonication of the left caudate head. The remaining 4 sessions were performed in clinic with sonication of the bilateral caudate heads using neuronavigation. The last session was followed by an MRI. Participants also completed assessments related to symptoms. On MRI, cerebral blood flow (CBF) of the caudate heads was assessed using arterial spin labelling (ASL). The study was approved by the VA R&D Committee and Stanford Institutional Review Board.
Results: Both participants (A, B) showed general improvement in the degree of pain interfering with daily functions on the Brief Pain Inventory (BPI) with Participant B showing more improvement. Participant A had more fluctuating pain severity scores on BPI (Fig). Participant B had more notable improvement with the most severe pain score of 9 at baseline to the score of 2 following the last LIFU session (Fig). Participant B also had improvement in the Migraine Disability Assessment Test (MIDAS) score, which decreased by 54% from 81 at baseline to 49 post-LIFU. On MRI, Participant B showed decreased CBF in the left caudate head post-LIFU with Ic/Ip of 0.48 from 0.81 pre-LIFU. Participant A had similar MIDAS scores before and after LIFU (64 and 68, respectively) and no notable trend in the caudate signal changes on ASL. No adverse effects were observed on symptom assessment and MRI.
Conclusion: This pilot study demonstrates that LIFU targeting of bilateral caudate heads for the treatment of PTH is feasible without notable adverse effects. One participant demonstrated substantial improvement in symptoms while the other patient had more equivocal results.

**Disclosures:** **B.C. Yoon:** None. **J.P. Coetzee:** None. **X. Kang:** None. **R. Brar:** None. **M. Timmerman:** None. **M.M. Adamson:** None.

**Poster**

**PSTR058. Ultrasound Neuromodulation Techniques**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR058.17/WW15

**Topic:** I.08. Methods to Modulate Neural Activity

**Support:** NCS-2220677

**Title:** Evaluating the safety of transcranial focused ultrasonic neuromodulation for applications to human subject cognitive control research

**Authors: *A. MYSORE**[1], C. BLAIS[1], W. J. TYLER[2], M. SANTELLO[1];
[1]Arizona State Univ., Tempe, AZ; [2]Univ. of Alabama, Birmingham, AL

**Abstract:** Transcranial-focused ultrasound stimulation (tFUS) can induce non-invasive neuromodulation at precise superficial and deep brain areas with an unparalleled high spatial and temporal resolution. At higher intensities and pulse/stimulation durations and lower

interstimulation intervals, tFUS causes heating in tissue. To explore the potential of tFUS as a prospective therapeutic and research technique, it is critical to systematically evaluate the safety of tFUS, especially with regard to tissue heating. To address this gap, we designed an ex-vivo experiment to test heating effects caused by tFUS using human cadaver skull fragments and soft tissue samples (chicken) by systematically modulating stimulation parameters. The experiment was set up in a temperature-insulated and acoustically-shielded water tank. The tFUS transducer was placed at the bottom of the tank facing upwards while an infrared camera was placed facing downwards to measure the change in the temperature of the tissue and/or skull placed between them. Custom 3D-printed clips held the hydrated human cadaver skull and/or a piece of chicken tissue between the transducer and camera. The stimulation was focused on the skull or tissue to evaluate tFUS-induced heating in both. Chicken breast was used to simulate neural tissue as its ultrasonic medium properties are similar to the human brain. Furthermore, the top surface of the tissue and/or skull was immersed in water to provide an ultrasonic medium similar to that encountered in a human tFUS experiment. The baseline tFUS parameters were 0.5 MHz acoustic frequency, 23.87 W/cm2 Isppa, 0.36-ms burst length, 1-ms period, 0.5-s stimulation duration and 2-s interstimulation duration. The tFUS parameters tested were within recommended safety limits of FDA for human stimulation. Three regions of interest were selected: a region encompassing the hot spot, one adjacent to that, and a region farthest away served as an ambient control for environmental changes in temperature. We found that all combinations of tFUS parameters induced heating of the skull and/or tissue ranging from 0.4 C to 2 C. It plateaued fastest in the skull-only no-soft tissue condition after ~ 13 min and took 53 min to plateau with the skull and soft tissue sample. As expected, the temperature increased at a higher rate and to a greater level at the skull than in the soft tissue. These observations regarding the thermal behavior of the skull and soft tissue during tFUS allow for the safe and effective creation of experimental protocols (tFUS for probing cognitive control mechanisms) as well as other research groups developing therapeutic applications of tFUS.

**Disclosures:** **A. Mysore:** None. **C. Blais:** None. **W.J. Tyler:** None. **M. Santello:** None.

**Poster**

**PSTR058. Ultrasound Neuromodulation Techniques**

**Location:** WCC Halls A-C

**Time:** Saturday, November 11, 2023, 1:00 PM - 5:00 PM

**Program #/Poster #:** PSTR058.18/WW16

**Topic:** I.08. Methods to Modulate Neural Activity

**Title:** Examination of low-intensity focused ultrasound (LIFU) parameters for human neuromodulation

**Authors: *A. N. ENNASR**[1,2], W. LEGON[2,3];
[1]Virginia Tech. Carilion Sch. of Med., Roanoke, VA; [2]Fralin Biomed. Res. Inst., Roanoke, VA; [3]Sch. of Neurosci., Virginia Tech., Blacksburg, VA

**Abstract:** Current animal studies examining LIFU parameters demonstrate conflicting results. Some suggest intensity and duration are the best predictors for neuromodulation effects in small animals, while others show duty cycle (DC) and pulse repetition frequency (PRF) in larger animals. The optimal LIFU parameters for robust, reproducible, lasting results in humans still need to be discovered. This is important for LIFU to translate to clinical and therapeutic options. This study aims to determine the optimal LIFU parameters for human neuromodulation. The first aim is to assess ultrasound parameters (intensity, duration, DC) on the primary motor cortex (M1) in healthy volunteers using motor evoked potential (MEP) analysis. The second aim is to compare the effects of pulsed vs. continuous wave (CW) applications of LIFU on MEPs. Full parameterization design includes two intensities, five DC, and two durations, resulting in 20 pulsed conditions along with four CW conditions. EMG will measure the first dorsal interosseous muscle after transcranial magnetic stimulation (TMS) of M1, with average MEP amplitude from 20 stimulations, per condition, as the primary outcome. To date, we have collected 10 healthy participants. There is a trend for a main effect of duration, such that 500 msec resulted in 14% (14% ± 35%) inhibition while 100 msec resulted in 3% (3% ± 39) inhibition ($p = 0.053$). There is also a trend for a duration x intensity interaction ($p = 0.10$). Specific parameter combinations look to have specific effects at the group level. For example, an intensity of 24 W/cm$^2$, DC of 1%, and a duration of 500msec inhibited MEPs by 25% (25% ± 24%). An intensity of 24 W/cm$^2$, DC of 50%, and a duration of 500msec trended towards 11% excitation (11% ± 45%) of MEPs. We also investigated the effect of pulsed vs CW LIFU, and there is currently no indication of any significant difference between these pulsing strategies. Overall, these results suggest that the effects of LIFU are mainly modulated by the duration parameter that may interact with intensity while DC may not have any impact. Controlling for total energy, LIFU applied in a pulsed or continuous fashion does not look to impact results. Investigating parameters and their effects is crucial for understanding the full potential of LIFU and translating LIFU as a clinical tool. Continued data collection is needed to better guide the research and clinical community about LIFU parameters. The next objective is to analyze the longevity of the LIFU parameters that show the most robust effects.

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